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The efficacy of ultrasound guided fascia iliaca block in hip fracture surgery: A systematic review and meta-analysis

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Abstract

Peripheral nerve blocks (PNBs) are effective techniques for perioperative pain control in hip fracture surgery. Various techniques of approaching the nerve have been demonstrated with ultrasound-guided approaches being implement in recent years due to its ability to identify the precise anatomy of the nerve. However, previous systematic review did not focus only ultrasound guided technique. This systematic review and meta-analysis aims to evaluate the efficacy of ultrasound-guided fascia iliaca compartment block (FICB) in adult patients undergoing hip fracture surgery. PubMed and Scopus databases as well as the references of included studies and previous systematic reviews were searched. The RCTs in adult hip fracture patient undergoing hip fracture surgery with standard anesthesia with ultrasound guided PNBs compared with no block or sham block as control were identified and included. The outcomes of interest were postoperative pain and opioid consumption. The mean differences (MD) were pooled with random-effect model. Pooled postoperative pain at 24 hr and 48 hr were lower in the intervention group compared to the control group. (MD -0.59, 95% CI -1.13,-0.05; I^2 90.78%, MD -0.99, 95%CI -1.74,-0.25; I^2 =95.28%, respectively). Postoperative opioid consumption was also lower in intervention group (MD -6.77, 95% CI -9.89,-3.66). Single shot injection showed lower pain scores than continuous injection in subgroup analysis. In conclusion, additional ultrasound guided FICB provided better postoperative pain control and decreasing opioid consumption in hip fracture surgery. Further researches are needed to demonstrate the effect of PNBs, especially focus on the technique of injection to confirm the robustness of the results.

Keywords : peripheral nerve block, hip fracture, postoperative pain, ultrasound guided, opioid consumption

1. Introduction

Hip fracture is a significant condition that debilitates the elderly population. The incidence of hip fracture worldwide has continuously increased (Cooper, Campion, and Melton, 1992), including in Thailand (Wongtriratanachai et al., 2013). One-year mortality were 45% in women and 60% in men (Rapp et al., 2008). Anesthetic management in hip fracture surgery can be either general or regional anesthesia with multimodal analgesia for perioperative pain control. Peripheral nerve block (PNBs) is beneficial in terms of better pain control, decrease dose of opioid and opioid related adverse events (Fabi, 2016). Guay (Guay et al., 2017) had shown that PNBs decreased pain scores by 3.4 on a scale from 0-10. Haddad and Williams (Haddad & Williams, 1995), Unneby (Unneby et al., 2017) and Jang (Jang et al., 2018) demonstrated the benefits of femoral nerve block (FNB) compare to no block in reduction of pain in hip fracture patients. Fujihara (Fujihara et al., 2013) and Yamamoto (Yamamoto et al., 2019) reported a significant decreased in pain scores in the fascia iliaca compartment block. Recently, Girón (Girón-Arango et al., 2018) proposed the latest technique, pericapsular nerve group block or PENG block. Lin (Lin et al., 2021) found that PENG provided superior pain control compare with FNB. Graham(Graham et al., 2008), Bang (Bang et al., 2016) and Shulte (Schulte et al., 2020) found no difference of pain

between PNBs and control group. However, these studies conducted PNBs under different approaches including landmark technique, nerve stimulation technique and ultrasound guided technique which can reflect the efficacy of nerve block. The recent meta-analysis (Guay & Kopp, 2020a) found that PNBs can reduce pain on movement by 2.5 on scale of 1-10. However, this review focused only on preoperative pain and did not exclusively focus on the use of ultrasound guided PNBs. Thereby, evidence of ultrasound guided PNBs in hip fracture surgery is still lacking.

2. Objectives

To evaluate the efficacy in terms of postoperative pain and opioid consumption of additional ultrasound guided fascia iliaca block compare with no block or sham block in hip fracture surgery.

3. Materials and methods

Search strategy

The relevant studies were identified from electronic databases including MEDLINE via PubMed, Scopus, references of selected articles, and references of previous systematic review. The search terms were constructed based on patient and intervention domain as follows: “hip fracture”, “intertrochanteric fracture”, “pertrochanteric fracture”, “femoral neck fracture”, “subtrochanteric fracture”, “nerve block”, “peripheral nerve block”, “fascia iliaca*”, “3-in-1 nerve block”, “femoral nerve*”, “pericapsular nerve group block”, “PENG block”, “anesthesia”, “analgesia”, “ultrasound guided”, “ultrasound guidance”. The search terms within each domain were combined with the Boolean operator “OR” and those between the domains with “AND”. The final search was done on October 31,2021. This review was a part of network meta-analysis of the efficacy of ultrasound guided peripheral nerve block techniques for perioperative outcome after hip fracture.

Inclusion criteria

A randomized control trial study of adult who diagnosed with closed hip fracture and underwent surgery under standard anesthesia combined with additional ultrasound-guided PNBs including FNB, FICB, 3-in-1 nerve block, PENG block, or combined nerve block compared with no block or sham block on postoperative pain and opioid consumption were included. The exclusion criteria included studies with insufficient data for pooling after 3 attempts of contacting author every 2 weeks, and studies published in languages which the reviewer could not translate.

Data extraction

Data extraction processes were performed independently by three reviewers (NK, PA and PN) using standardized data extraction form. The data extraction form comprised of three major parts which are general characteristic of study, characteristic of subject, and outcome results.

Risk of bias assessment

The risk of bias (RoB) was assessed independently by three reviewers (NK, PA and PN) following The Cochrane Risk of Bias tool for randomized trials (RoB2.0)(Sterne et al., 2019). The following five domains will be assessed: randomization, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as “low risk”,” high risk” and “some concerns” risk of bias. The study was judged as high RoB if at least one of these domains was rated at high risk; low RoB if all domains were judged as low risk; otherwise, the study was judged as

some concerns RoB. Any disagreement will be discussed and make a consensus between the reviewers.

Statistical analysis

Stata software version 16.1 was used for the meta-analysis. Mean differences (MD) with 95% confidence interval (CI) were used to assess postoperative pain score and opioid consumption. The meta-analysis was conducted when 3 or more trials reported the same outcomes. The heterogeneity was assessed by I^2. Random effect model was used if $I^2 > 25$; otherwise, a fixed-effect model was used. Heterogeneity was explored by meta-regression and subgroup analysis according to administration technique (single shot vs continuous) were done.

4. Results

4.1 Characteristic of selected studies

A total of 8 RCTs were taken into the meta-analysis. (Diakomi et al., 2020; Hao et al., 2019; Ma et al., 2018; Mostafa et al., 2018; Schulte et al., 2020; Thompson et al., 2020; Yamamoto et al., 2019; Yang, 2016) The basic characteristic, intervention and co-intervention were summarized in Table 1. Mean age ranged from 58 to 84.7 years and female accounted for about 30% to 88%. The ASA physical status class III ranged from 24% to 95.45%, with regional anesthesia technique of 31.17% to 100%. Anesthetic agent commonly used for nerve block was ropivacaine.

4.2 Risk of bias

According to 5 domains of Cochrane RoB: 5,7,8,5,7 studies out of 8 studies were consider as low RoB for randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result, respectively (Table.2). Five of out eight studies were judged as low RoB, 1 and 2 studies as some concerns and high RoB, respectively.

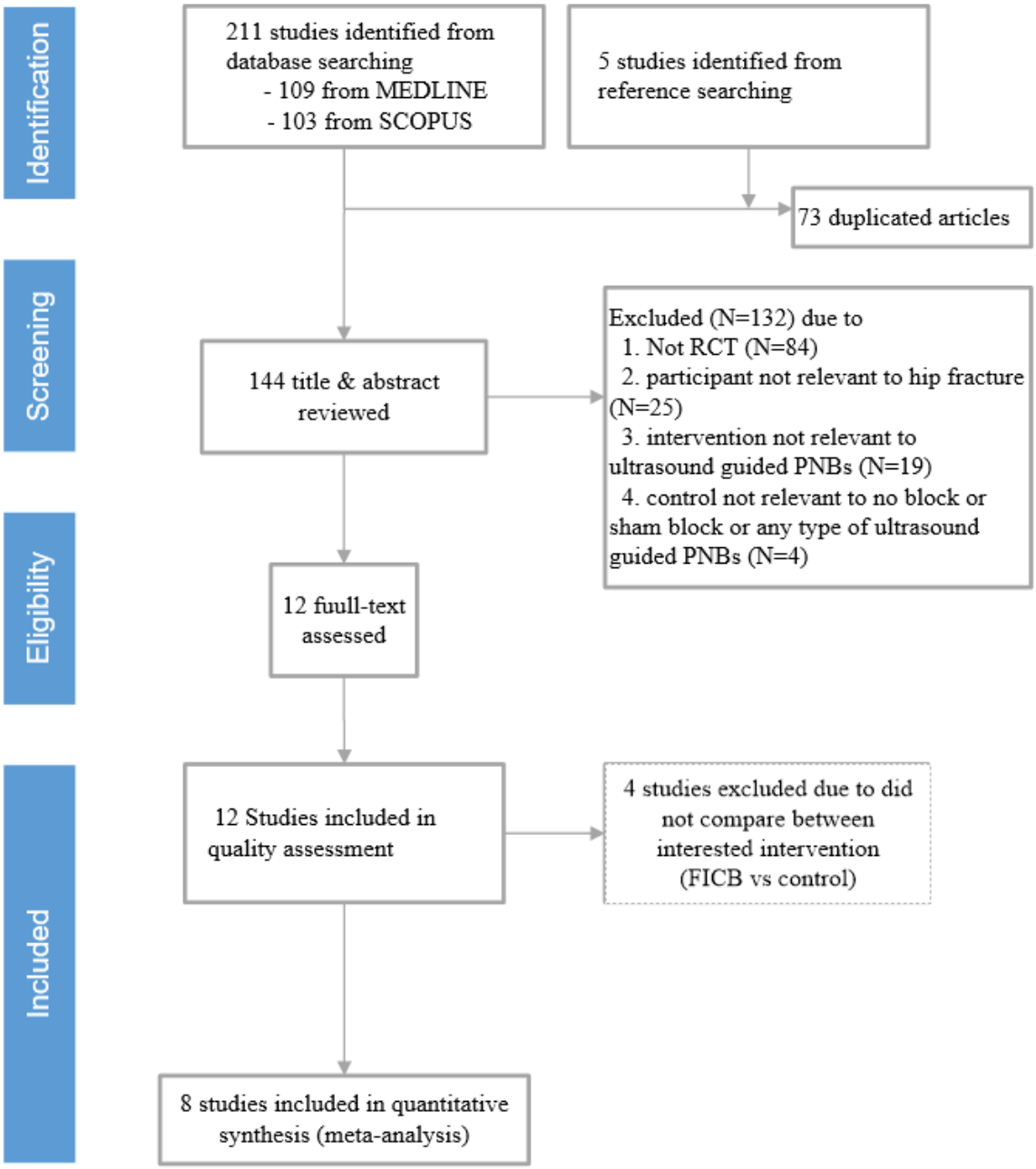


Figure 1 Flow diagram of included studies

Table 1 Characteristics of included studies

Study	Intervention	Start of intervention	End of nerve block	Comp-arator	Mean Age	% Female	Mean BMI	%ASA class >II	% Extra capsular fracture	% RA	LA	Concentration of LA	Duration of surgery (mins)	Co-intervention
Yang, 2016	cFICB	OR	3days	No block	NR	NR	NR	NR	NR	0	Ropi	Mixed	NR	IV PCA sufentanil
Mostafa et al, 2018	cFICB	OR	2days	No block	58.85	30	NR	NR	NR	0	Levo	Low	131.85	IV fentanyl (intraop) IV paracetamol IV pethidine 20 mg. (rescue)
Ma, 2018	cFICB	ED	preop	No block	83.89	65.91	NR	93.18	NR	100	Ropi	Mixed	88.66	SA + EA IV PCA sufentanil
Thomson, 2019	FICB	OR	Single shot	No block	81.43	70.2	NR	NR	74.28	38.41	Ropi	High	NR	Standard multimodal analgesia, paracetamol, tramadol, morphine
Yamamoto, 2019	FICB	OR	Single shot	No block	84.65	85.07	21	NR	60.36	100	Levo	High	NR	Loxoproxen 60 mg. PO, diclofenac suppo 25 mg.
Hao, 2019	cFICB	AD	preop	Sham block	72.41	45.85	NR	32.9	57.64	100	Ropi	Mixed	NR	Fentanyl 0.05 mg IM PCEA 48 hr
Shulte, 2020	FICB	OR	Single shot	No block	75.5	28.8	NR	57.85	60.85	0	Ropi	High	NR	Opiate and non-opiate medication
Diakomi, 2020	FICB	OR	Single shot	Sham block	78.1	68.68	25.45	28.02	71.98	100	Ropi	High	NR	IV PCA tramadol

cFICB= continuous fascia iliaca compartment block, FICB= fascia iliaca compartment block, cFNB= continuous femoral nerve block, FNB= femoral nerve block, OR= operative room, ED= emergency department, AD= admission, preop= before operation , NR= not reported, Ropi= ropivacaine, Bupi= bupivacaine, Levo= levobupivacaine, low= concentration <0.25%, high= concentration >0.25%, mixed= both high and low concentration, PCA= patient control analgesia, SA= spinal anesthesia, EA= epidural anesthesia, PCEA=patient control epidural anesthesia, PO= per oral, IM=intramuscular, IV= intravenous

Table 2 Risk of bias of included studies

Author	Year	Randomisation process	Deviation from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	overall
Yang J	2016						
Mostafa SF	2018						
Ma Y	2018						
Thomson J	2019						
Yamamoto N	2019						
Hao J	2019						
Shulte SS	2020						
Diakomi M	2020						

= Low risk = High risk = Unclear

4.3 Meta-analysis

Postoperative pain at 24 hr

Seven studies out of 8 studies reported postoperative pain at 24 hr. Five hundreds and ninety-seven participants were analyzed and evaluated post operative pain at 24 hr. the intervention was FICB compared with no block or sham block. Pain scores were lower with FICB (MD -0.59, 95% CI -1.13,-0.05; I^2 90.78%). Subgroup analysis according to technique of administration (single shot vs continuous) were also assessed to explore source of heterogeneity. Single shot nerve block had lower pain score at 24 hr, MD -1.17 (95%CI -2.6, -0.26) while continuous nerve block had minimal effect MD -0.06 (95%CI -0.18,0.05). (Figure 2A)

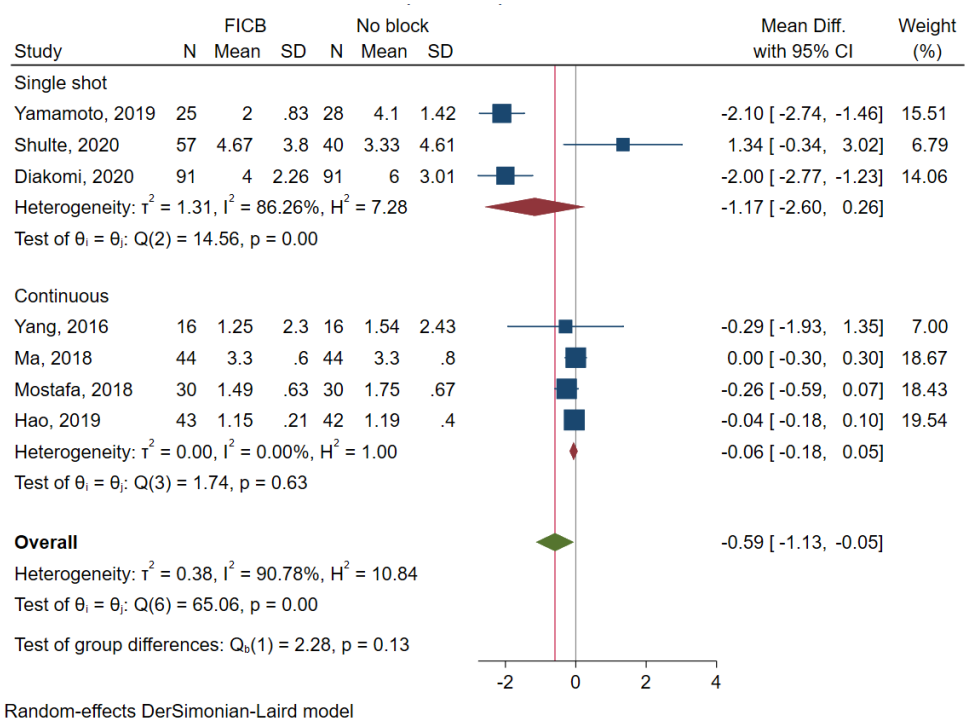
Postoperative pain at 48 hr

Six studies out of 8 studies reported post operative pain at 48 hr which included 537 participants. Pain scores were lower in FICB group (MD -0.99, 95%CI -1.74,-0.25; I^2 =95.28%). Single shot administration of nerve block demonstrated lower pain score (MD -1.97, 95%CI -3.29, -0.65) compared with continuous nerve block (MD -0.99, 95%CI -1.74, -0.25). (Figure 2B)

Postoperative opioid consumption

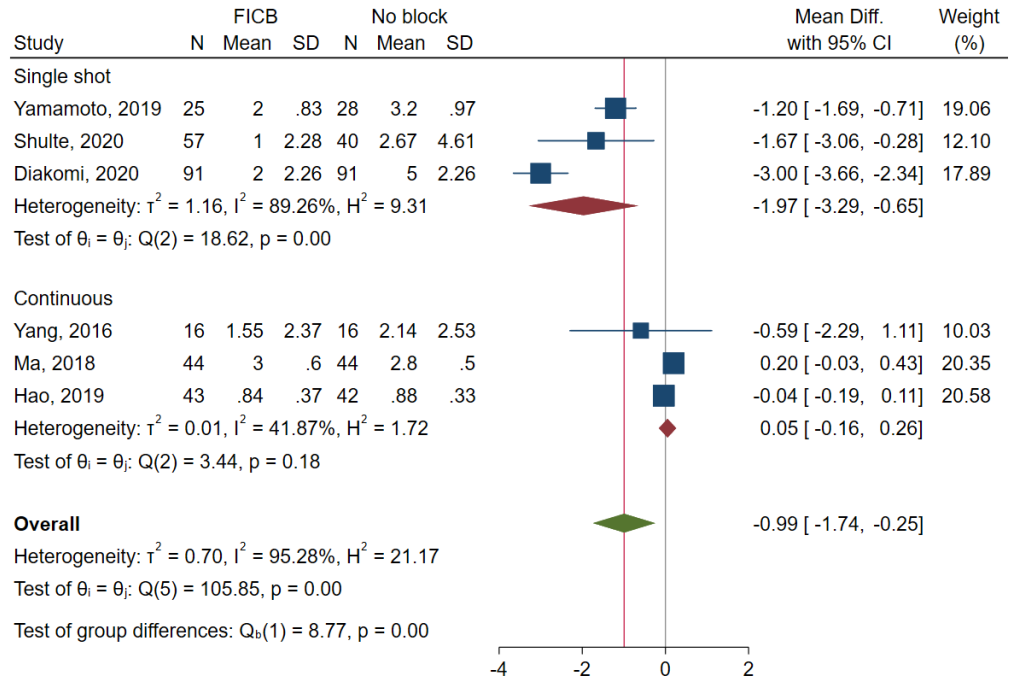
Only five studies out of 8 studies reported postoperative opioid consumption. Four hundreds seventy-one participants were analyzed. Total opioid requirement (mg of morphine) was significantly lower in FICB group compare with control (MD -6.77, 95% CI -9.89,-3.66). However, the heterogeneity was high. (Figure 3)

Figure 2A Forest plot of postoperative pain at 24 hr



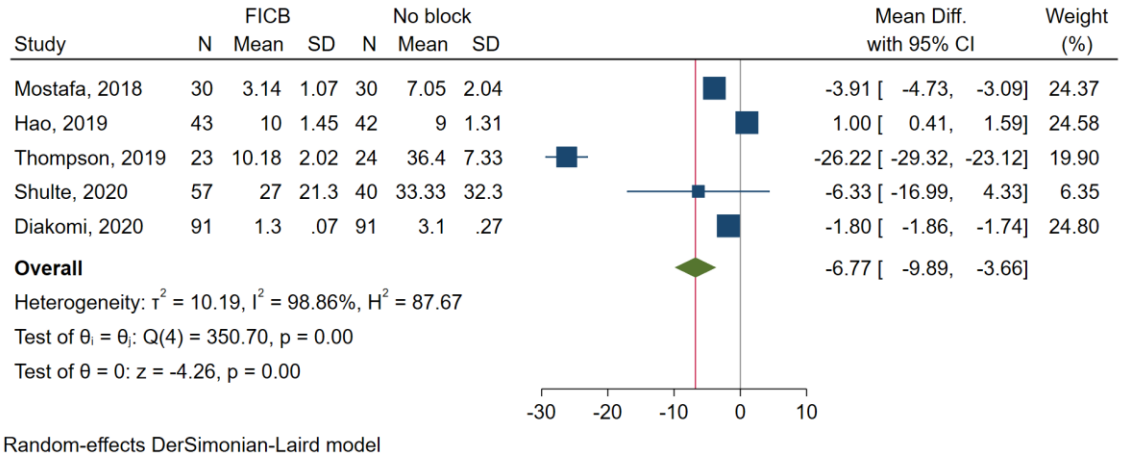
Random-effects DerSimonian-Laird model

Figure 2B Forest plot of postoperative pain at 48 hr



Random-effects DerSimonian-Laird model

Figure 3 Forest plot of postoperative opioid consumption



5. Discussion

This meta-analysis was performed to investigate the efficacy of additional ultrasound guided FICB compared with no block on postoperative pain and opioid consumption. Our results found statistically significant lower in postoperative pain at 24 and 48 hr as well as total opioid consumption between FICB compared with no block.

The results showed in the same direction compared to subgroup analysis of FICB in previous systematic review(Guay & Kopp, 2020b) in the aspect of pain score (MD -1.17, 95%CI -1.42,-0.92) but the previous review focus only post nerve block pain and most of the studies located nerve by landmark technique, which in theory using imaging or ultrasound guide to deliver the medication should be more efficacious.

Subgroup analysis according to injection technique (single shot vs continuous) demonstrated larger effect size of decreasing pain scores from single shot injection compared with continuous infusion in both 24 and 48 hr postoperatively. These may explain by multiple reasons. Firstly, about the volume of injection, it is possible that the larger volume of single shot injection reached further along the fascial planes compared with continuously small volume of infusion in the same plane. Secondly, the sophisticated continuous technique that use the catheter to deliver the medication and postoperative catheter care, including proper position of catheter, well secured catheter which allowed patient's ambulation, kinking catheter causing obstruction, may also reflect the outcomes.

For postoperative opioid consumption, according to systematic review of Ritcey (Ritcey et al., 2016), five out of sixes studies demonstrated a statistically significant reduction in consumption of opiates with a regional nerve block. The meta-analysis could not be performed in this previous systematic review. In this systematic review and meta-analysis, we found the significant reduction of opioid consumption in FICB group compared with no block (MD -6.77, 95%CI -9.89,-3.66).

The strength of this review was that we focused on ultrasound guided PNBs which is becoming common technique in clinical practice as the ultrasound equipments and personnel expertise are becoming available, and could be the standard of care in the future. However, there were also the limitation of this study. Firstly, there were still small number of studies included and the quality of some study could still be questionable. Secondly, there were high heterogeneity in most outcomes and subgroup analysis could explain only small degree of heterogeneity, in which other unmeasured factors could still be the source of heterogeneity.

Thirdly, pain score was a subjective measurement, therefore could be biased by the measurement in an unblinded clinical trial. Finally, the choice of anesthesia, including general anesthesia, spinal, or epidural anesthesia, as well as comprehensive co-intervention of pain control protocol which integrated varying multimodal analgesia in each study, also had an effect on both pain scores and opioid consumption. Future clinical trials, with proper sample sizes and objective measurements should be done to confirm our findings.

6. Conclusion

This meta-analysis results support the advantage of PNBs on better postoperative pain control and decrease opioid consumption in hip fracture surgery. Single shot nerve block showed better performance compare with continuous nerve block. The results suggested that single short nerve block may be adequate for postoperative pain control in hip fracture surgery. Further researches are needed to demonstrate the effect of PNBs, especially focus on the technique of injection to confirm the robustness of the results.

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Implementation of the Infection Control Program in CoViD-19 Management in a District Hospital in Negros Occidental

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Abstract

This descriptive paper analyzed the extent of implementation of an infection control program in Covid-19 management in Cadiz City District Hospital in Negros Occidental during CY 2021. This program revolves around the job performance of 210 HCW-respondents, who were dominated by the young, married, and shorter-tenured hospital employees. Needed data were collected using a self-made research instrument that has passed the tests of validity and reliability. The ensuing data analyses revealed analogous findings of "great extent" in the implementation of the infection control programs, specified by respondents' groupings by age, civil status, and length of service. Other notable findings include HCWs' diligence in wearing face masks/shields and their consistent adherence to the smoking hospital policy but leaving so much to be desired in the donning and doffing of personal protective equipment (PPE). A subsequent comparative analysis on standard precaution obtained a significant difference in the extent of implementation of the same program based on groupings by age and length of service (LOS), but the extreme opposite came out when respondents were grouped by civil status. On environmental control, the opposite emerged: A significant difference was found when respondents were grouped by civil status. Nonetheless, no such difference was found in groupings by age and LOS, including the area on waste management. These findings call for hospital leadership to strictly enforce physical distancing during waste segregation, regularly evaluate and monitor areas receptive to improvement, and establish a checklist of hospital preparedness to meet exigencies like the Covid-19 pandemic.

Keywords : Health protocols, infection control program, covid-19 management, standard precautions, environment control, waste management, Cadiz City, Negros Occidental

1. Introduction

There is a need for a new, critical worldview on health as a component of human progress, security, and rights. This has so far been the assertion of experts named Williams and Maruthappu (2013) in their paper that saw print in the American Journal of Public Health. This worldwide imperative has taken the front seat due to the outbreak of COVID-19, cogently described by Sempowski, Saunders, Acharya, Wiehe, and Haynes (2020) to have caused frantic worldwide efforts from the government, academe, and even the private sector to rapidly develop countermeasures to bring this health condition back to normalcy.

It is by now common knowledge that COVID-19 is an infectious disease caused by a newly discovered coronavirus, which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China. It was initially reported to the World Health Organization (WHO) on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency. On March 11, 2020, the WHO subsequently declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009. The name was chosen to avoid stigmatizing the virus's origins in populations, geography, or animal associations.

The WHO reported that as of March 22, 2021, the overall infected individual worldwide is over 21 million. From the Department of Health COVID 19 Tracker, the number of cases in the Philippines is 80,970, which is 12.1% of active cases. 577,850 are recovered cases which are 86%, and 12,972 cases of death, which is 1.93% of the total cases; as expected, these present cases are expected to increase in the months due to poor adherence to the minimum standard health protocols. In Western Visayas, the total confirmed cases of COVID 19 are 28, 214, with recoveries of 25, 663 and mortality of 731 with an overall case fatality rate of the virus of 2.59%. The Cadiz District Hospital had 834 cases, 277 of them were active cases, with total recoveries of 731, and mortality of 39 among admitted patients (WHO, Western Pacific, 100 Days Of Covid 19 In The Philippines, May 2020).

Faced with this threatening contagion, hospitals like the Cadiz District Hospital in Negros Occidental, Philippines had to resort to standard precaution, environmental control, and waste management to contain COVID-19. The foregoing areas were considered the basic Infection Prevention Control Precautions (IPCP) in the current health care system. In essence, standard precautions are the minimum infection prevention practices that apply to all patient care, regardless of the patient's suspected or confirmed infection status, in any setting where health care is delivered. Environmental control is the adaptation of the workplace's physical enhancement and modifies cleaning schedules, maintenance work, patient placement, and ventilation. On the other hand, waste management is the importance of healthcare sanitation in preventing the spread of infections within the healthcare worker and place. (Infection Prevention and Control of Epidemic- and Pandemic-Prone Acute Respiratory Infections in Health Care, WHO, 2019)

As head of the Infection Control Section of the Identified COVID 19 Facility, the present researcher initiated this study to evaluate the implementation of the infection control program in COVID-19 management to assess the areas that need improvement to continue saving lives in the service to humanity. This motivated the researcher to conduct the study, which will help elevate the awareness of the employees and take steps to prevent the spread of infection and ensure the safety of themselves, the patients, and the community.

1.1 Objectives

This study aimed to determine the extent of the implementation of the infection control program (ICP) in CoViD-19 management in Cadiz District Hospital, Cadiz City, Negros Occidental, during the Calendar Year 2020. Specifically, it sought answers to the following questions: 1. What is the extent of the implementation of the infection control program (ICP) in COVID-19 management when respondents are grouped according to standard precaution, environmental control, and waste management? 2. What is the extent of the implementation of the ICP in COVID-19 management when respondents are grouped according to age, civil status, and length of service? 3. What is the extent of implementation of the ICP in COVID-19 management when respondents are grouped according to the variables above? 4. Is there a significant difference in the extent of the implementation of the ICP program in COVID-19 management when the respondents are grouped and compared according to the same variables mentioned above?

1.2 Hypothesis

There is no significant difference in the extent of implementation of the ICP in COVID-19 management when respondents are grouped and compared according to the variables earlier mentioned.

2. Related Research

This section presents the body of knowledge with bearings on the infection control program inCOVID-19 management.

2.1 Hand Washing

The standard precaution in preventing in-hospital transmission of COVID 19 is hand washing or the use of alcohol-based hand rubs. Healthcare workers who are the frontline fighters have direct contact with the Covid-19 positive patients; thus, the importance of hand hygiene in preventing the spread of infection should be strictly imposed. This is supported by the study of Araghi in August 2020, on "Hand Hygiene Among Health Care Workers During COVID-19 Pandemic: Challenges and Recommendations". The study explains that hand hygiene is of utmost importance for the prevention of COVID-19 among HCWs. This can be achieved by applying alcohol-based hand rubs, washing hands properly with soap and water, and applying other antiseptic agents. The study by Hillier, on April 2020, "Using effective hand hygiene practice to prevent and control infection," reiterates that decontamination using hand hygiene remains one of the most important and effective methods for reducing healthcare-associated infections and cross-infection between patients.

2.2 Mask-wearing

Another study by Qing-Xia Ma on "Potential utilities of mask-wearing and instant hand hygiene for fighting SARS-CoV-2" in September 2020 explains that mask-wearing and hand washing can slow the spread of the virus. The efficacy of three types of masks and instant hand wiping was evaluated, and the result showed that instant hand wiping using a wet towel soaked in water containing one percent soap powder or active chlorine removed 99.98% of the virus from hands, respectively. On the other hand, face masks and face shields were considered preventive measures in limiting the spread of COVID-19 in health care settings. Thus according to Cotrin et al.'s study dated October 2020, on "The Use of Facemasks during the COVID-19 Pandemic by the Brazilian Population", reported that among all the participants wearing facemasks, 34% complied because it is mandatory, and 65% continue to wear facemask even if it was not required. Meanwhile, most participants believe that the use of masks effectively prevents the spread of novel coronavirus infections. Further, almost all subjects were wearing masks in crowded and public places. On the contrary, 67% of the respondents are bothered with facemasks due to discomfort such as feeling trapped or suffocated.

Based on Macintyre's study on " Facemasks for the prevention of infection in healthcare and community settings," in April 2018, results concluded that masks were used for respiratory protection of well people. It is found that facemasks alone or facemasks plus hand hygiene may prevent infection in community settings. Healthcare workers favored respirators for clinical respiratory illness. The use of reusable cloth masks is widespread globally, particularly in Asia, an essential region for emerging infections. On the other hand, in January 2019, according to A. Chughtai on "Current practices and barriers to the use of facemasks and respirators among hospital-based health care workers in Vietnam," highlighted that the use of facemasks and respirators is not continuous, but rather is limited to selected situations, locations, and patients. Reuse of facemasks and respirators is also common, and some participants reported believing that the reuse of facemasks, particularly cloth masks, is safe.

In contrast, others believed that the reuse of masks put staff at risk of infection. Furthermore, from the same analytical findings of the author, on May 2019 on "Availability, consistency and evidence base of policies and guidelines on the use of mask and respirator to protect hospital health care workers: a global analysis," concluded that mask is used to

protect healthcare workers against seasonal influenza for the low-risk situation and use of a respirator for high-risk situations. These recommendations were uniformly made by the World Health Organization (WHO) and the Center for Disease and Control (CDC) to protect healthcare workers. However, for pandemic influenza and SARS, the WHO recommends mask use in low risk and respirators in high-risk situations. In contrast, the CDC recommends respirators in both low and high-risk situations.

2.3 Work Attitudes and Perceptions

Healthcare worker attitudes and perceptions on infection control also play a role in handling infectious disease or COVID-19 patients. Approach and understanding the preventive measures in the hospital setting for newly emerging pandemic require more profound understanding and knowledge. From the study of Reuben, July 2020, "Knowledge, Attitudes, and Practices Towards COVID-19: An Epidemiological Survey in North-Central Nigeria, "The knowledge, attitudes, and practices (KAP) of the people toward COVID-19 is critical to understanding the epidemiological dynamics of the disease and the effectiveness, compliance, and success of IPC measures adopted in a country. The majority of the respondents had positive attitudes toward the adherence to government IPC measures, such as practicing social distancing or self-isolation, improved personal hygiene, and using face masks. Results for the assessment of respondents' attitudes believed that everyone should wear a face mask. Most reported protective measures against COVID-19 identified by most respondents included proper hygiene, self-isolation or social distance, face mask or gloves, and prayers.

According to Chu (2020) on “Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis,” the transmission of viruses was lower with the physical distancing of 1 meter or more, compared with a distance of less than one meter. The protection was increased as the distance was lengthened. The use of face masks results in a large reduction in risk of infection, with stronger associations with N95 or similar respirators compared with disposable surgical masks or similar. The use of eye protection is also associated with less infection.

2.4 Environmental Control and Waste Management

Environmental Control and Waste Management are also the cornerstones of the Infection Prevention Control Program in the Hospital setting. The chain of infection from the initial exposure to its spread to the environment and the appropriate disposal should be adequately established by a health care facility, especially in the emergence of infectious diseases or pandemic surges. Therefore, according to Moi Lin Ling in 2018, in the review of the “Asia Pacific Society of Infection Control (APSIC) Guidelines for Environmental Cleaning and Decontamination" showed that best practices should be optimized in routine cleaning and decontamination in healthcare facilities, management of patients with isolation precautions, food preparation areas, construction, and renovation. It recommends implementing an environmental hygiene program to keep the environment safe for patients, staff, and visitors visiting a healthcare facility. There should also be an assessment of facility cleanliness and recommendations for secure handling of linen and bedding and occupational health and safety issues. It also recommends the involvement of a training program to ensure consistent adherence to best practices.

Moving on, Polverino (2020) studied “Cigarette Smoking and COVID-19: A Complex Interaction,” This paper showed that the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease (COVID-19), mainly affect the lung and the prevalence of current smokers among hospitalized patients with COVID-19 has

been reported consistently lower than the prevalence of smokers among the general population. The study concludes that cigarette smoke is detrimental to the lungs in several ways. The effect of current smoking on SARS-CoV-2 infection is a delicate and complex topic that should be addressed meticulously.

The study of Xie et al. (2021) on "COVID-19 and smoking: What evidence needs our attention," concludes that despite the COVID-19 epidemic, the findings suggested that COVID-19 has not encouraged smokers to quit. The result showed that isolation at home has contributed to increased smoking behavior and increased quantities. Therefore, governments recommend that governments increase smoking cessation messaging as part of public health measures to contain the COVID-19 pandemic. According to Ahmed et al.'s research on "Tobacco smoking a potential risk factor in the transmission of COVID-19 infection," May 2020 concluded that smoking tobacco is a possible mode of transmission for the virus for both active and passive smokers. Smoking should be considered a risk factor for disease transmission until further evidence and measures to limit its direct and indirect effects should be implemented within the community.

In the Philippines, Mitchel and Barker's (2017) study on "Infection control at an urban hospital in Manila showed that early stages of interventions should include efforts to understand perceptions held by healthcare workers who participate in infection control programs. Further, an effective Infection control program comprises a long-standing infection control committee, a dedicated infection control nursing staff, and innovative electronic hand hygiene surveillance technology. On the other hand, barriers include sub-optimal dissemination of hand hygiene compliance data, high nursing turnover, clinical time constraints, and resource limitations that restricted equipment purchasing. A systems engineering approach helps conduct a comprehensive work system analysis and maximize resources to overcome known barriers to infection control in heavily resource-constrained settings.

Meanwhile, Wake (2020) investigated good knowledge, positive attitude, and good practice towards COVID-19 respective to their age, educational level, residence, monthly income, profession, gender, marital status, and news media. The result reported a good level of knowledge, an optimistic attitude, and a good level of practice about COVID-19. It was suggested that community education should support improving the knowledge, attitude, and practice of the population. Training should be provided for healthcare workers to update and make them more effective in diagnosing, managing, and controlling this pandemic. The integration of good knowledge, a positive attitude, and good practice towards COVID-19 also contribute a significant and essential role in controlling this pandemic. The healthcare workers are at the frontline defense against the COVID-19 pandemic; thus insufficient knowledge, negative attitude, and poor practice can significantly affect the management and control of this pandemic. Insufficient knowledge and negative attitudes directly affect the practice and lead to poor infection control, the spread of the virus, delayed diagnosis, and increased morbidity and mortality.

In a study by Stary last January 2020 on "Infectious Diseases: The Role of the Healthcare Professional," findings showed that adopting standard precautions prevents transmission and other infectious diseases. Healthcare professionals should wash their hands before and after contact with each patient. Strategies include a copy of good hand washing techniques displayed by the sink in the medical room, placement of a mounted liquid soap from a wall, alcohol hand rub can be used as an alternative if hands are dry and physically clean. Staff should wear gloves when exposed to body fluids, mucous membranes, or non-intact skin when cleaning up body fluids or handling clinical waste, including contaminated

laundry. Also, cover any fresh wounds less than 24 hours old, open skin lesions, or exposed skin with a waterproof dressing. The result of using single gloves has been reduce the risk of acquiring infection.

3. Methodology

This section presents the research design, local of the study, respondents of the study, the data gathering instrument, the data-gathering procedure, analytical schemes, and the statistical tools.

3.1 Research Design

This paper used the descriptive research design to determine the extent of awareness and implementation of ICP in the COVID 19 management. In the words of Kowalycsyk (2015), this design is capable of describing the people involved in the research and can be done using an observational, case study, or survey.

3.2 Study Respondents

The respondents of this study are all 210 doctors, nurses, and midwives of Cadiz District Hospital. These health care providers are identified from the list of personnel at the Nursing and Medical Office.

3.3. Data Gathering Instrument

The instrument used in gathering the data was a self-made questionnaire that has passed the tests of validity and reliability.

3.4 Data Gathering Procedure

After establishing the validity and reliability of the instrument, the researcher wrote a letter to the Chief of Hospital asking permission to administer the questionnaire to the respondents. The researcher identified the respondents, explain the purpose of the study, and gave instructions on how to accomplish objectively and honestly the questionnaires. Upon approval, the researcher administered the questionnaire to the respondents and carefully guided the respondents to answer the needed data. The researcher personally retrieved the questionnaires. Then the data were categorized, tabulated, and prepared for statistical treatment.

3.5 Data Analysis

Objectives 1 and 2 used the descriptive analytical scheme while objective 3 used the comparative analytical to carry out those predetermined objectives in the introductory section of this paper. Statistical tools used include frequency and percentage count, mean, and Mann-Whitney U test.

5. Results and Discussion

This chapter presents, analyzes, and interprets the data that were gathered to carry out the pre-determined objectives of this study.

5.1 Respondents' Profile

When analyzed in terms of age, civil status, and length of service, the respondents' profile shows a 55:45 ratio in favor of the younger ones, a 59:41 ratio in favor of the married group, and another 59:41 ratio favoring those with a shorter length of service.

5.2 Extent of Implementation of Infection Control Program (ICP) in COVID-19 Management based on Standard Precaution, Environmental Control, and Waste Management

Table 1 Extent of Implementation of ICP in COVID-19 Management based on Standard Precaution

Items	Mean	Interpretation
1. Face shield and face mask must be worn at all times	4.95	Very Great Extent
2. Thorough hand washing must be observed before and after handing the patient or any procedure	4.30	Great Extent
3. Staff should observe standard precautions and limit patient exposure	4.45	Great Extent
4. NO PPE or incomplete PPE, NO DUTY. Therefore, appropriate endorsement, inventory, and completeness of the identified needs of the staff per station should be strictly observed.	4.43	Great Extent
5. Donning and Doffing of the PPE's should be done by a trained observer with the supervision of any available senior staff on duty.	3.42	Moderate Extent
6. Alcohol-based hand rubs must be used to clean hands between patient contaorct	4.60	Very Great Extent
7. All staff are expected to wear their complete duty uniforms or scrubs	4.81	Very Great Extent
8. Bending or recapping of the needle is not allowed; perform the scoop method	4.67	Very Great Extent
9. Designated areas for covid suspect, probable, and positive to prevent cross-contamination.	4.16	Great Extent
10. Gloves have to be used for each patient and must be disposed of after each patient interaction	3.77	Great Extent
Overall Mean	**4.36**	**Great Extent**

Table 1 summarizes the analysis on the extent of implementation of ICP in COVID-19 management focusing on standard precaution obtaining an overall mean score of 4.36, interpreted to mean "great extent." When items are taken individually, item number 1 yielded the highest mean of 4.95, verbally interpreted to mean "very great extent." This validates the assumption that hospital personnel are adherent to the ICP protocol of the hospital, especially on the face mask. Comparatively, item number 5 received the lowest mean of 3.42, interpreted to mean "moderate extent." This is because most hospital staff have no proper or previous training on donning and doffing. Likewise, senior staff in charge is hesitant to assist due to fear of exposure to the virus, coupled with limited knowledge of the procedure. Overall, these correlate with Chu's (2020) research that the use of face masks, respirators, and eye protection in public and health care settings should be optimized.

Table 2 Extent of Implementation of ICP in COVID-19 Management based on nvironmental Control

Items	Mean	Interpretation
1. Room used by patients with mild to moderate symptoms suggested of Covid 19 must undergo thorough mechanical cleaning and disinfection	4.54	Very Great Extent
2. Filter of air conditioners are cleaned once a month or as recommended	3.80	Great Extent

Items	Mean	Interpretation
3. Environmental Measures that must be followed includes cleaning frequently touched surfaces and objects, including cellphones, gadgets, tables, doorknobs, and desks.	4.42	Great Extent
4. Maintaining the environment clean, especially common-use areas and those with touchpoints such as railings, staircases, light switches, and the like.	2.52	Moderate Extent
5. Open windows daily to allow air to circulate in hospital rooms. This will also dry up damp spaces more easily.	4.47	Great Extent
6. In waiting areas, maintaining a distance between symptomatic and non-symptomatic patients (3 feet), in addition to source control measures, may limit exposures.	4.38	Great Extent
7. The methods for handling, transporting, and laundering soiled textiles are determined	2.84	Moderate Extent
8. Eating alone and not in a group	4.48	Great Extent
9.Proper isolation techniques were observed by staff	4.14	Great Extent
10. No smoking within hospital vicinity	4.81	Very Great Extent
Overall Mean	**4.04**	**Great Extent**

Table 2 shows the “great extent” of implementation of ICP in Covid-19 management with an overall mean score of 4.04. Item no. 10 yielded the highest mean score 4.81, interpreted to mean “very great extent.” This validates hospital stakeholders’ strict compliance with Republic Act No. 9211, an omnibus law regulating smoking in public places. Moreover, this finding relates to Ahmed et al.’s (2020) study on "Tobacco smoking as a potential risk factor in the transmission of COVID-19 infection." On the other hand, item no. 4 registered the lowest mean score of 2.52, which means “moderate extent.” This result suggests that everyone’s in harm’s way in the hospital’s vicinity; and thus, gives room for Weber and Sickbert-Benneth’s (2019) study on the "Continuous room decontamination technologies.” To the duo, the contaminated surface environment in the rooms of hospitalized patients is an important risk factor for the colonization and infection of patients with multidrug-resistant pathogens.

Table 3 Extent of Implementation of ICP in COVID-19 Management based on Waste Management

Items	Mean	Interpretation
1.Proper waste segregation is strictly observed	4.61	Very Great Extent
2. Hazardous waste and general waste must not be mixed	4.61	Very Great Extent
3.Infectious waste must be placed in a yellow-colored plastic bag with a biohazard symbol	4.76	Very Great Extent
4.Disposable needles and sharps should be discarded in puncture-resistant containers	3.65	Great Extent
5.Safe handling and disposal of clinical waste using proper PPE	4.77	Very Great Extent
6. Waste generated from infected patients isolated and quarantined should be treated as hazardous and require special care while putting	4.80	Very Great Extent

Items	Mean	Interpretation
in storage containers and during collection and final disposal		
7, Strict hygiene protocol among utility workers from segregation of waste to disposal	4.10	Great Extent
8. Physical distancing between healthcare workers during waste segregation	3.36	Moderate Extent
9.Proper discharge of pollutants in the atmosphere and water needs to be regulated to avoid disease transmission and pollution to the environment.	4.39	Great Extent
10. Waste should be removed and disposed of regularly	4.72	Very Great Extent
Overall Mean	**4.38**	**Great Extent**

Table 3 illustrates the overall mean of 4.38, duly interpreted to mean "great extent" of implementation of ICP. Items 6 and recorded the highest and lowest mean scores of 4.80 while item no. 8 got a mean score of 3.36 is at the bottom of all items. The latter deals with physical distancing between healthcare workers during waste segregation. When analyzed closely, the result coincides with the existing protocol of the infection control program of the Cadiz District Hospital, wherein all waste generated by infectious patients was considered hazardous and, subsequently, needs to be handled with extreme care. As a point of emphasis, waste segregation needs regular monitoring, as individual manual effort is required due to limited equipment used in the process of waste management.

5.3 Extent of ICP Implementation in COVID-19 Management based on Standard Precaution, Environmental Control, and Waste Management and Groupings by Age

Table 4 Extent of Implementation of ICP in COVID-19 Management based on Standard Precaution and Age Groupings

Items	Younger		Older	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1. Face shield and face mask must be worn at all times	5.00	Very Great Extent	4.89	Very Great Extent
2. Thorough hand washing must be observed before and after handing the patient or any procedure	4.53	Very Great Extent	4.01	Great Extent
3. Staff should observe standard precautions and limit patient exposure	4.28	Great Extent	4.66	Very Great Extent
4. NO PPE or incomplete PPE, NO DUTY. Therefore, appropriate endorsement, inventory, and completeness of the identified needs of the staff per station should be strictly observed.	4.39	Great Extent	4.48	Great Extent
5. Donning and Doffing of the PPE's should be done by a	3.27	Moderate Extent	3.61	Great Extent

Items	Younger		Older	
trained observer with the supervision of any available senior staff on duty.				
6. Alcohol-based hand rubs must be used to clean hands between patient contact	4.59	Very Great Extent	4.60	Very Great Extent
7. All staff are expected to wear their complete duty uniforms or scrubs	4.91	Very Great Extent	4.69	Very Great Extent
8. Bending or recapping of a needle is not allowed; perform the scoop method	4.67	Very Great Extent	4.67	Very Great Extent
9. Designated areas for a covid suspect, probable, and positive to prevent cross-contamination.	3.72	Great Extent	4.71	Very Great Extent
10. Gloves have to be used for each patient and must be disposed of after each patient interaction	3.86	Great Extent	3.65	Great Extent
Overall Mean	**4.32**	**Great Extent**	**4.40**	**Great Extent**

Table 4 shows the overall mean of 4.32 for the younger group and 4.40 for the older group, both duly interpreted to mean "great extent" of implementation of ICP in COVID-19 management based on standard precaution and age groupings. Item 1 stood out with a perfect mean score of 5.0 for the younger group and 4.89 for the more aged group. This shows how diligent hospital personnel are in wearing face masks. Saqlain's (2020) paper corroborates this result with their own findings that healthcare workers have positive attitude and practice regarding COVID-19, and perceived that limited infection control material and poor knowledge regarding transmission as the major barriers to infection control. Comparatively, item 5 on the donning and doffing of PPEs obtained the lowest mean scores of 3.27 (moderate extent) for the younger group and 3.61 (great extent) for their more aged counterparts.

Table 7 Extent of ICP Implementation in COVID-19 Management based on Environmental Control and Groupings by Age

Items	Younger		Older	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1.Room used by patients with mild to moderate symptoms suggested of Covid 19 must undergo thorough mechanical cleaning and disinfection	4.25	Great Extent	4.89	Very Great Extent
2.Filter of air conditioners are cleaned once a month or as recommended	3.66	Great Extent	3.97	Great Extent
3. Environmental Measures that must be followed includes cleaning frequently touched surfaces and	4.60	Very Great Extent	4.19	Great Extent

Items	Younger		Older	
objects, including cellphones, gadgets, tables, doorknobs, and desks.				
4. Maintaining the environment clean, especially common-use areas and those with touchpoints such as railings, staircases, light switches, and the like.	2.58	Moderate Extent	2.45	Low Extent
5. Open windows daily to allow air to circulate in hospital rooms. This will also dry up damp spaces more easily.	4.45	Great Extent	4.49	Great Extent
6. In waiting areas, maintaining a distance between symptomatic and non-symptomatic patients (3 feet), in addition to source control measures, may limit exposures.	4.22	Great Extent	4.57	Very Great Extent
7. The methods for handling, transporting, and laundering soiled textiles are determined	2.93	Moderate Extent	2.72	Moderate Extent
8. Eating alone and not in a group	4.53	Very Great Extent	4.41	Great Extent
9.Proper isolation techniques were observed by staff	4.18	Great Extent	4.10	Great Extent
10. No smoking within hospital vicinity	5.00	Very Great Extent	4.59	Very Great Extent
Overall Mean	**4.04**	**Great Extent**	**4.04**	**Great Extent**

Table 5 shows an identical overall mean of 4.04 for both younger and more aged groups, duly interpreted to mean "great extent" of implementation of ICP based on environmental control and age groupings. Standing out is item no. 10 garnering a towering mean score of 5.0 for the young and 4.59 for the not so young. The findings illustrate how compliant both age groupings are in Republic Act 9211 or with smoking prohibition in hospital vicinity. Comparatively, item no. 4 obtained the lowest of 2.58 for the young and 2.45 for their more aged counterparts, duly interpreted to mean "moderate extent" and "low extent," respectively. This means that both groups were unable to maintain the cleanliness of the environment clean, and this may be due to the fear of exposing themselves to the common areas and touchpoints exposed to covid 19 patients. Additionally, most of the older groups have co-morbidities that hinder them from exposing themselves to infectious areas.

Table 6 Extent of Implementation of ICP in COVID-19 Management based on Waste Management and Groupings by Age

Items	Younger		Older	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1.Proper waste segregation is strictly observed	4.66	Very Great Extent	4.55	Very Great Extent
2. Hazardous waste and general waste must not be mixed	4.63	Very Great Extent	4.60	Very Great Extent

Items	Younger		Older	
3.Infectious waste must be placed in a yellow-colored plastic bag with a biohazard symbol	4.79	Very Great Extent	4.71	Very Great Extent
4.Disposable needles and sharps should be discarded in puncture-resistant containers	3.72	Great Extent	3.55	Great Extent
5.Safe handling and disposal of clinical waste using proper PPE	4.74	Very Great Extent	4.81	Very Great Extent
6. Waste generated from infected patients isolated and quarantined should be treated as hazardous and require special care while putting in storage containers and during collection and final disposal	4.74	Very Great Extent	4.86	Very Great Extent
7, Strict hygiene protocol among utility workers from segregation of waste to disposal	4.13	Great Extent	4.06	Great Extent
8. Physical distancing between healthcare workers during waste segregation	3.38	Moderate Extent	3.33	Moderate Extent
9.Proper discharge of pollutants in the atmosphere and water needs to be regulated to avoid disease transmission and pollution to the environment.	4.26	Great Extent	4.54	Very Great Extent
10. Waste should be removed and disposed of regularly	4.67	Very Great Extent	4.78	Very Great Extent
Overall Mean	**4.37**	**Great Extent**	**4.38**	**Great Extent**

Table 5 shows an almost identical overall mean of 4.37 for the young and 4.38 for the not so young, duly interpreted to mean “great extent” of implementation of ICP based on waste management and age groupings. Among the stated Items, the numerical mean score of Item no. 6 got the highest mean score of 4.86 for the older group and 4.74 for their younger counterparts. Expectedly both got an interpretation of “very great extent.” These figures would mean due diligence in treating wastes generated from infected, quarantined patients as hazardous, requiring special care in collection and disposal of the same. More than that, this shows awareness of health care workers that improper or poor healthcare waste management can result in serious environmental and human health risks.

On the flip side, the sole item that showed an interpreted mean of “Moderate Extent,” was garnered by Item no. 8, which reads, “Physical distancing between healthcare workers during waste segregation,” with a numerical mean score of 3.38 for the younger group and 3.33 for the younger group respectively. This finding explains that there is poor compliance in the minimum health protocol, which is maintaining the physical distancing when it comes to waste segregation. This is because the bulk of waste materials are being disposed of daily, and manual manpower is utilized during the process. Equipment needed for waste disposal is limited in the facility, and the level of understanding of the personnel handling the waste is

poor or limited. Health education should be given regularly, especially for personnel that expose themselves to infectious areas.

5.4 Extent of Implementation of ICP in COVID-19 Management based on Standard Precaution, Environmental Control, and Waste Management when grouped by Civil Status

Table 7 Extent of the Implementation of ICP in COVID-19 Management based on Standard Precaution and Groupings by Civil Status

Items	**Single**		**Married**	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1. Face shield and face mask must be worn at all times	5.00	Very Great Extent	4.92	Very Great Extent
2. Thorough hand washing must be observed before and after handing the patient or any procedure	4.29	Great Extent	4.31	Great Extent
3. Staff should observe standard precautions and limit patient exposure	4.41	Great Extent	4.48	Great Extent
4. NO PPE or incomplete PPE, NO DUTY. Therefore, appropriate endorsement, inventory, and completeness of the identified needs of the staff per station should be strictly observed.	4.31	Great Extent	4.51	Very Great Extent
5. Donning and Doffing of the PPE's should be done by a trained observer with the supervision of any available senior staff on duty.	3.36	Moderate Extent	3.46	Moderate Extent
6. Alcohol-based hand rubs must be used to clean hands between patient contact	4.64	Very Great Extent	4.56	Very Great Extent
7. All staff are expected to wear their complete duty uniforms or scrubs	5.00	Very Great Extent	4.69	Very Great Extent
8. Bending or recapping of a needle is not allowed; perform the scoop method	4.70	Very Great Extent	4.65	Very Great Extent
9. Designated areas for a covid suspect, probable, and positive to prevent cross-contamination.	3.99	Great Extent	4.28	Great Extent
10. Gloves have to be used for each patient and must be disposed of after each patient interaction	3.95	Great Extent	3.64	Great Extent
Overall Mean	**4.37**	**Great Extent**	**4.35**	**Great Extent**

Table 7 shows an overall mean of 4.37 for single respondents and 4.36 for their married counterparts in the extent of the implementation of ICP in COVID-19 management based on standard precaution and groupings by civil status. Both are verbally interpreted as "great extent." Item no. 1 got the highest mean score of 5.0 for the singles and 4.92 for the married group. The result validates the expectation that both the single and married group religiously complies with the use of facemask at all times, when inside the hospital premises, a result corroborated by Cotrin et al. (2020) on "The Use of Facemasks during the COVID-19 Pandemic by the Brazilian Population." The said study showed that almost all participants are wearing facemasks because it is mandatory, and prevent the spread of coronavirus and are worn mostly in crowded and public places.

Far south, item no. 5 registered the lowest mean of 3.46 for the married group and 3.36 for the unmarried, all interpreted to mean "moderate extent." It would seem clear that donning and doffing of personal protective equipment (PPE) are the hospital's inherent weaknesses, which is the result of lack of ample training. This finding validates Rajamani et al.'s (2020) paper that to prevent infections among HCWs, there should be proper training, timely procurement of PPE stocks, and responding appropriately to suspected cases.

Table 8 Extent of Implementation of ICP in COVID-19 Management based on Environmental Control and Groupings by Civil Status

Items	**Single**		**Married**	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1.Room used by patients with mild to moderate symptoms suggested of Covid 19 must undergo thorough mechanical cleaning and disinfection	4.49	Great Extent	4.57	Very Great Extent
2.Filter of air conditioners are cleaned once a month or as recommended	3.71	Great Extent	3.85	Great Extent
3. Environmental Measures that must be followed includes cleaning frequently touched surfaces and objects, including cellphones, gadgets, tables, doorknobs, and desks.	4.67	Very Great Extent	4.24	Great Extent
4. Maintaining the environment clean, especially common-use areas and those with touchpoints such as railings, staircases, light switches, and the like.	2.45	Low Extent	2.56	Moderate Extent
5. Open windows daily to allow air to circulate in hospital rooms. This will also dry up damp spaces more easily.	4.49	Great Extent	4.45	Great Extent
6. In waiting areas, maintaining a distance between symptomatic and non-symptomatic patients (3 feet), in addition to source control measures, may limit exposures.	4.31	Great Extent	4.42	Great Extent
7. The methods for handling,	2.94	Moderate	2.77	Moderate

Items	Single		Married	
transporting, and laundering soiled textiles are determined		Extent		Extent
8. Eating alone and not in a group	4.62	Very Great Extent	4.39	Great Extent
9.Proper isolation techniques were observed by staff	4.50	Very Great Extent	3.90	Great Extent
10. No smoking within hospital vicinity	4.95	Very Great Extent	4.72	Very Great Extent
Overall Mean	**4.11**	**Great Extent**	**3.99**	**Great Extent**

Table 8 shows an overall mean of 4.11 (single group) and 3.99 (married group) in the extent of the implementation of ICP in COVID-19 management based on environmental control and still on the same groupings by civil status. Both are verbally interpreted "great extent." Like in the previous tables, item no. 10 stood out by getting the highest mean of 4.95 for the singles and 4.72 for the married ones. This means that both married and single group adheres to the no-smoking rules within the hospital premises. This is corroborated by Xie et al. (2021) on "COVID-19 and smoking: What evidence needs our attention," which concludes that despite the COVID-19 epidemic, the findings recommended that government should increase smoking cessation messaging as part of public health measures to contain the COVID-19 pandemic. Down south, item no. 4 garnered the lowest mean scores of 2.56 and 2.45 for the married and singles, respectively. This implies that both the single and married groups were somehow remiss in their duties of maintaining the cleanliness of the common areas exposed by infectious patients probably because of the fear of contracting the virus themselves. The existence of this fear among health workers is confirmed by Kaur et al. (2020) that the transmission of the virus takes place either directly through close contact with an infected individual or indirectly by touching contaminated surfaces. The said study reports that virus survives on the surfaces from few hours to days.

Table 9 Extent of Implementation of ICP in COVID-19 Management based on Waste Management and Groupings by Civil Status

Items	Single		Married	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1.Proper waste segregation is strictly observed	4.64	Very Great Extent	4.5	Very Great Extent
2. Hazardous waste and general waste must not be mixed	4.58	Very Great Extent	4.64	Very Great Extent
3.Infectious waste must be placed in a yellow-colored plastic bag with a biohazard symbol	4.80	Very Great Extent	4.73	Very Great Extent
4.Disposable needles and sharps should be discarded in puncture-resistant containers	3.71	Great Extent	3.60	Great Extent
5.Safe handling and disposal of clinical waste using proper PPE	4.76	Very Great Extent	4.78	Very Great Extent
6. Waste generated from infected patients isolated and quarantined should be treated as hazardous and require special care while putting in storage containers and during	4.67	Very Great Extent	4.88	Very Great Extent

Items	Single		Married	
collection and final disposal				
7, Strict hygiene protocol among utility workers from segregation of waste to disposal	4.07	Great Extent	4.12	Great Extent
8. Physical distancing between healthcare workers during waste segregation	3.37	Moderate Extent	3.35	Moderate Extent
9.Proper discharge of pollutants in the atmosphere and water needs to be regulated to avoid transmission of disease and pollution to the environment.	4.23	Great Extent	4.49	Very Great Extent
10. Waste should be removed and disposed of in a regular basis	4.65	Very Great Extent	4.77	Very Great Extent
Overall Mean	**4.35**	**Great Extent**	**4.39**	**Great Extent**

Table 9 shows an overall mean of 4.35 for the single group and 3.99 fior the married group in the extent of the implementation of ICP in COVID-19 management based on solid waste management and still on the same groupings by civil status. Again, both scores are verbally interpreted as "great extent." The singles scored the highest at 4.80 in item no. 3 on the task of placing infectious waste materials in a yellow plastic bag with a bio-hazard symbol. The married ones scored the highest at 4.77 in item no. 10 on the task of removing and disposing of wastes on a regular basis. On the flip side, both groups scored the lowest in item no. 8 at 3.37 for the singles and 3.35 for their married counterparts. This item talked about physical distancing between healthcare workers (HCWs) during waste segregation. HCWs are somewhat remiss with this function of adhering to the maintenance of minimum health protocols. This is probably because a lot of waste materials are disposed of every day, the ratio of HCW to the number of daily waste disposal is in proportion, thus maintaining the physical distancing in handling the heavy infectious wastes is poorly practiced in the hospital premises. Bruin (2020) supports this HCWs' predicament as social or physical distancing was duly encouraged, as well as keeping a safe distance of 1-2 meters.

5.5 Implementation of ICP in COVID-19 Management based on Standard Precaution, Environmental Control, and Waste Management and Groupings by Length of Service

Table 10 Extent of Implementation of ICP in COVID-19 Management based on Standard Precaution and Groupings by Length of Service

Items	Shorter		Longer	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1. Face shield and face mask must be worn at all times	5.00	Very Great Extent	4.89	Very Great Extent
2. Thorough hand washing must be observed before and after handing the patient or any procedure	4.52	Very Great Extent	3.99	Great Extent
3. Staff should observe standard precautions and limit patient exposure	4.24	Great Extent	4.74	Very Great Extent

Items	Shorter		Longer	
4. NO PPE or incomplete PPE, NO DUTY. Therefore, appropriate endorsement, inventory, and completeness of the identified needs of the staff per station should be strictly observed.	4.41	Great Extent	4.45	Great Extent
5. Donning and Doffing of the PPE's should be done by a trained observer with the supervision of any available senior staff on duty.	3.24	Moderate Extent	3.68	Great Extent
6. Alcohol-based hand rubs must be used to clean hands between patient contact	4.58	Very Great Extent	4.62	Very Great Extent
7. All staff are expected to wear their complete duty uniforms or scrubs	4.88	Very Great Extent	4.72	Very Great Extent
8. Bending or recapping of the needle is not allowed; perform the scoop method	4.67	Very Great Extent	4.68	Very Great Extent
9. Designated areas for a covid suspect, probable, and positive to prevent cross-contamination.	3.67	Great Extent	4.85	Very Great Extent
10. Gloves have to be used for each patient and must be disposed of after each patient interaction	3.83	Great Extent	3.68	Great Extent
Overall Mean	**4.30**	**Great Extent**	**4.43**	**Great Extent**

Table 10 shows an overall mean of 4.30 for the shorter-tenured group and 4.43 for the longer-tenured group in the extent of the implementation of ICP in COVID-19 management based on standard precaution and groupings by length of service (LOS). Again, both scores are verbally interpreted "great extent." As shown in the table, item 1 scored the highest at 5.0 for the shorter-tenured group (STG) and 4.89 for the longer-tenured group (LTG), and both mean "very great extent" of implementation specifically on the diligent wearing of face shields and face masks. The result means that regardless of the length of service, both groups seriously consider wearing these equipment to be extremely necessary.

As shown on the same table, item no. 5, which reads, "Donning and doffing of the PPE's should be done by a trained observer with the supervision of any available senior staff on duty," got the lowest mean score, of 3.24 for the STG and 3.68 for the LTG. The former's score means "moderate extent" while the latter means "great extent" of implementation.

The findings confirmed Rajamani et al.'s (2020) paper that adherence to guidelines of PPE preparedness, HCW training, procuring PPE stocks, and responding appropriately to suspected cases is crucial to prevent infections in HCWs.

Table 11 Extent of ICP Implementation in COVID-19 Management based on Environmental Control and Groupings by Length of Service

Items	Shorter		Longer	
	Mean	Interpretation	Mean	Interpretation
1.Room used by patients with mild to moderate symptoms suggested of Covid 19 must undergo thorough mechanical cleaning and disinfection	4.32	Great Extent	4.85	Very Great Extent
2.Filter of air conditioners are cleaned once a month or as recommended	3.67	Great Extent	3.98	Great Extent
3. Environmental Measures that must be followed includes cleaning frequently touched surfaces and objects, including cellphones, gadgets, tables, doorknobs, and desks.	4.52	Very Great Extent	4.28	Great Extent
4. Maintaining the environment clean, especially common-use areas and those with touchpoints such as railings, staircases, light switches, and the like.	2.59	Moderate Extent	2.41	Low Extent
5. Open windows daily to allow air to circulate in hospital rooms. This will also dry up damp spaces more easily.	4.40	Great Extent	4.56	Very Great Extent
6. In waiting areas, maintaining a distance between symptomatic and non-symptomatic patients (3 feet), in addition to source control measures, may limit exposures.	4.29	Great Extent	4.49	Very Great Extent
7. The methods for handling, transporting, and laundering soiled textiles are determined	2.88	Moderate Extent	2.78	Moderate Extent
8. Eating alone and not in a group	4.56	Very Great Extent	4.37	Great Extent
9.Proper isolation techniques were observed by staff	4.24	Great Extent	4.00	Great Extent
10. No smoking within hospital vicinity	4.99	Very Great Extent	4.56	Very Great Extent
Overall Mean	**4.05**	**Great Extent**	**4.03**	**Great Extent**

Table 11 illustrates the result of the analysis with an almost identical overall mean of 4.05 fr STG and 4.03 for LTG on the extent of ICP implementation in COVID-19 management focusing on environmental control. The result proves once more the adherence of HCW on the hospital's no smoking policy, evidenced by the highest mean of 4.99 and 4.56 for the LTG and STG, respectively. This finding shows, among others, that level of HCW's awareness of the ill effects of smoking consistent with Polverino's (2020) study entitled,

"Cigarette Smoking and COVID-19: A Complex Interaction" and Ahmed et al.'s (2020) research on, "Tobacco smoking a potential risk factor in the transmission of COVID-19 infection." Nonetheless, special attention needs to be given on the maintaining a clean environment in item number 4, which recorded the lowest mean of 2.59 for the STG and 2.41 for the LTG, respectively. This connects with Adhikari et al.'s (2020) research on the need of several public health measures that may prevent or slow down the transmission of the COVID-19, i. e. case isolation, identification, and follow-up of contacts, environmental disinfection, and use of personal protective equipment. The study concluded that the best prevention is to avoid being exposed to the virus.

Table 12 Extent of ICP Implementation in COVID-19 Management based on Waste Management and Groupings by Length of Service

Items	**Shorter**		**Longer**	
	Mean	**Interpretation**	**Mean**	**Interpretation**
1.Proper waste segregation is strictly observed	4.69	Very Great Extent	4.49	Very Great Extent
2. Hazardous waste and general waste must not be mixed	4.66	Very Great Extent	4.55	Very Great Extent
3.Infectious waste must be placed in a yellow-colored plastic bag with a biohazard symbol	4.81	Very Great Extent	4.68	Very Great Extent
4.Disposable needles and sharps should be discarded in puncture-resistant containers	3.61	Great Extent	3.70	Great Extent
5.Safe handling and disposal of clinical waste using proper PPE	4.76	Very Great Extent	4.79	Very Great Extent
6. Waste generated from infected patients isolated and quarantined should be treated as hazardous and require special care while putting in storage containers and during collection and final disposal	4.76	Very Great Extent	4.84	Very Great Extent
7, Strict hygiene protocol among utility workers from segregation of waste to disposal	4.07	Great Extent	4.14	Great Extent
8. Physical distancing between healthcare workers during waste segregation	3.38	Moderate Extent	3.32	Moderate Extent
9.Proper discharge of pollutants in the atmosphere and water needs to be regulated to avoid transmission of disease and pollution to the environment.	4.28	Great Extent	4.53	Very Great Extent
10. Waste should be removed and disposed of on a regular basis	4.70	Very Great Extent	4.75	Very Great Extent
Overall Mean	**4.37**	**Great Extent**	**4.38**	**Great Extent**

Table 12 illustrates the result of the analysis with another roughly identical overall mean of 4.37 for STG and 4.38 for LTG on the extent of ICP implementation in COVID-19

management focusing on waste management. The LTG scored the highest at 4.84 while the STG got 4.76 in item no. 6, which reads, "Waste generated from infected patients isolated and quarantined should be treated as hazardous and require special care while putting in storage containers and during collection and final disposal." Both scores mean "very great extent" of implementation. This connects well with Sankhan's (2020) study that recommended that medical waste generated by clinics, wards, specialized examination rooms, and medical laboratories should be regarded as medical waste related to COVID-19 and should be placed into double yellow or red medical waste bags. Comparatively, both groups scored the lowest at 3.38 for STG and 3.34 for LTG in item number 8 that talked about the need for physical distancing between healthcare workers during waste segregation. The foregoing findings are corroborated by Sankham (2020), which recommended HCWs to wear medical masks, gloves, protective clothing, and waterproof shoes.

5.6 Significant Difference in Standard Precaution, Environmental Control, and Waste Management in ICP Implementation in COVID-19 Management based on Selected Variables Groupings

Table 13 Difference in Standard Precaution in ICP Implementation in COVID-19 anagement based on Selected Variable Groupings

Variable	Category	N	Mean Rank	Mann Whitney U-test	p-value	Sig. level	Interpretation
Age	Younger	116	97.72	4549.500	0.038	0.05	Significant
	Older	94	115.10				
Civil Status	Single	86	106.73	5226.500	0.806		Not Significant
	Married	124	104.65				
Length of Service	Shorter	123	94.78	4032.500	0.002		Significant
	Longer	87	120.65				

Table 13 summarizes the analysis in standard precaution relative to ICP implementation in COVID-19 management. At 0.05 level of significance, a significant difference was found when respondents were grouped by age and length of service. On the contrary, no such significant difference was found when the same respondents were grouped by civil status.

Table 14 Difference in Environmental Control in ICP Implementation in COVID-19 Management based on Selected Variable Groupings

Variable	Category	N	Mean Rank	Mann Whitney U-test	p-value	Sig. level	Interpretation
Age	Younger	116	106.60	5324.500	0.770		Not Significant
	Older	94	104.14				
Civil Status	Single	86	121.76	3933.500	0.001	0.05	Significant
	Married	124	94.22				
Length of Service	Shorter	123	107.81	5066.500	0.510		Not Significant
	Longer	87	102.24				

Table 14 summarizes the analysis in environmental control relative to ICP implementation in COVID-19 management and focusing on the very same variable

groupings. A contrasting result was found showing no significant difference when respondents were grouped by age and length of service. In contrast, a significant difference was found when the same respondents were grouped by civil status.

5.7 Difference in Waste Management in ICP Implementation in COVID-19 Management based on Selected Variable Groupings

The ensuing analysis on the difference in waste management relative to ICP implementation in COVID 19 management showed no significant difference when respondents were grouped by age, civil status, and length of service. The null hypothesis in the introductory section is, henceforth, accepted.

6. Conclusion

This research brought the spotlight on the extent of implementation of an infection control program in Covid-19 management in the Cadiz District Hospital in Cadiz City. Negros Occidental during the CY 2021. This program revolves around and is reflected by the job performance of 210 HCW-respondents dominated by the young, married, and shorter-tenured hospital employees. Data analyses revealed analogous findings of "great extent" in the implementation of the infection control programs, specifically on standard precautions, environment control, and waste management specified by respondents' groupings by age, civil status, and length of service. Other notable findings include HCWs' diligence in wearing face masks/shields and consistent adherence to the smoking hospital policy but leaves so much to be desired in the donning and doffing of personal protective equipment (PPE). A comparative analysis on standard precaution showed a significant difference in the extent of implementation of the same program based on groupings by age and length of service (LOS), but the extreme opposite came out when respondents were grouped by civil status. On environmental control, the opposite emerged: A significant difference was found when the same respondents were grouped by civil status. Nonetheless, no such difference was found in groupings by age and LOS, including the program area on waste management. These findings call for hospital leadership to pay close attention to the need to strictly enforce physical distancing during waste segregation, regular evaluation and monitoring of areas receptive to improvement, and the establishment of a checklist of hospital preparedness to meet exigencies like the Covid-19 pandemic.

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8. Biodata

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Aging-Related Resiliency: Process, Relevance, and Evidence

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Abstract

Contrary to the belief of increasing physical dependency and frailty among older adults, the concept of resilience narrates how they bear a positive outlook to address difficulties based on a cumulative and constructed problem-solving learning approach. Despite studies that implicate resilience to successful coping among older adults, understanding the process, relevance, and evidence of resilience in this population is warranted. This academic paper synthesizes related studies on aging-related resiliency as a process that is relevant to the adaptive coping of older adults evidenced by a positive outlook amidst the challenges of aging. Recovery from age-related changes starts with the acknowledgment of change in health status. As an effect, responses provide an overview of how older adults cope effectively based on a learned pattern of solving encountered problems. Resilience, while subjective, is exemplified by the utilization of adaptive coping strategies, and available resources to reduce the deleterious consequences of aging. Evidence of older adult resiliency is seen when a positive outlook and adaptive coping lead to favorable outcomes. In the light of resilience among older adults, this process involves a series of continuous adaptation to changes that coincide with aging and other related factors while acknowledging the use of available coping strategies and resources for successful aging. Future studies must examine the developmental process of resilience to provide translation of this concept into practice by testing resilience in the context of older adults in the practice of gerontology nursing.

Keywords: aging, coping, frailty, gerontology, resilience

Introduction

In the face of frailty and connotations of decreased functional capacity among older adults, establishing independence in activities of daily living has been one of the features of successful aging (Andersen et al., 2019). Despite challenges in the evident decline of bodily processes, a positive coping to control age-related morbidity is essential (Moore et al., 2015; Martinez-Moreno et al., 2020). With coping, the term resilience is associated with the individual's capacity to navigate through adversities to bring about favorable outcomes (Feliciano et al., 2022; Angevaare et al., 2020).

Studies have included resilience as an essential and crucial factor to overcome the challenges of aging. Regarded as a process, it allows the strengthening of both intrinsic and extrinsic characteristics to utilize the most appropriate strategies to address individual situations (Aburn et al., 2016). Due to the possibility of cognitive decline, loss of essential bodily processes, physical dependency, and Related symptoms can have a substantial impact on one's quality of life and everyday activities. Complications can arise from simple symptoms of aging inclusive of depression, sensory deficits, and major cardiovascular and respiratory conditions. Understanding insomnia among older adults, for instance, can lead to depression (Treszise et al., 2018), and can provide interventions to ensure that common health ailment is acknowledged early in its course.

Despite claims of resilience being associated with coping, successful aging, and quality of life among adults, the subjective nature of this concept brings about challenges in

understanding its value with respect to older adults' status, adversities, needs, and coping. As it is integral to the person's current and prior understanding of distressing events, resilience has been poorly concretized and manifested in the context of older adults. Understanding the initiation of the process, its relevance to adaptive coping, and manifestations of resilience can highlight relevant measures to integrate this concept into the practice of gerontology.

Synthesized in this academic paper is the conception of aging-related resiliency as a process that is relevant to the adaptive coping of older adults evidenced by a positive outlook despite adversities and challenges of aging. Triggered by physical, functional, and psychological limitations in a significant area of an older adult's daily living (Feliciano et al., 2022), acknowledgment of change starts the process of resilience, an intricate pattern of utilizing adaptive coping mechanisms with a positive outlook to recover from adversities. This section provides an understanding of this process, its relevance to adaptive coping with appropriate strategies and available resources, and the manifestations of aging-related resiliency through a positive outlook and coping with adversities.

Process

As a process, resilience starts with responses to distressing events that overview older adults' impression to adapt and recover positively. Knowing what to expect and how to access potential coping strategies provides a higher likelihood of recovery from age-related life challenges (Sörensen et al., 2021). Should older adults respond to distressing events in this manner, adapting to change and positive recovery from the situation are guaranteed? To continually progress, positive management of deleterious events and their consequences (e.g., hospitalization, bereavement, loss of spouse) must be met with adequate sustenance (MacLeod et al., 2016). Part of the growth and development of individuals is to acknowledge the eventual decline and gain of new abilities and processes with respect to different phases in life (Fuller & Huseth-Zosel, 2021). Conscious effort to acknowledge changes molds the person's perspective and decision to accept them or not. The manifestation of acceptance can be seen through responses to distressing events which places older adults to establish equilibrium and deal with difficult situations that threaten overall development (Timalsina & Songwathana, 2020; Masten, 2014). Consequently, these responses overview the older adults' impression to adapt and recover successfully based on an adequate understanding of the situations around them.

The ongoing learning experiences of older adults have been established during younger years and their refinement to initiate adaptive coping skills has led to constructive and reinforced adaptation to present and future challenges (MacLeod et al., 2016). As an effect, older adults tend to have a wide range of coping mechanisms to provide adequate and objectively defined resilience (Golant, 2015).

Relevance

Resilience is a form of adaptive coping which is exemplified by individually appropriate strategies and resources. While frailty has been associated with older adults' decline in physiological responses along with the emergence of complex health issues (Xu et al., 2019), a strengthened and constructed outlook allows them to resiliently cope with adversities far beyond how younger counterparts perform (Li & Ow, 2022).

Managing and recovering from the serious consequences of stressful events, the focus of interventions is to enhance coping, and resilience and to return to individually appropriate levels of optimal functioning (Fontes & Neri, 2015). Successful aging is based on the identification and focus of dimensions to specifically identify where to promote older adult

health (Estebsari et al., 2020). As a process, resiliency is enhanced when strategies and resources are adequate to meet the demands of aging and its challenges (Aburn et al., 2016). Similarly, the assimilated coping strategies are aligned with available resources that are acceptable to older adults (Fontes & Neri, 2015). To address their needs as aligned with potential strategies, understanding the older care needs is crucial (Abdi et al., 2019).

Evidence

Positive outlook and coping are evidence of older adult resiliency. Simply put, resiliency refers to the capacity of an individual to manage adversities in a manner that protects health and well-being and supports quality of life (Kiosses & Sachs-Ericsson, 2020). Its specific value lies in the attached meaning of demanded interventions to implicate successful recovery from challenges (Angevaare et al., 2020). Regarded as a dynamic capacity toward successful aging, the context of older adult resiliency is implicated in the intricate relations of several dimensions, namely physiological, mental, emotional, and psychosocial performance. It is a health asset that reflects the older adults' positive outlook and coping amidst the future loss of essential bodily processes. It is an intricate process than a personality trait (MacLeod et al., 2016) that culminates with the person's ability to develop over time.

Physical and functional evaluation of older adults can also be used to identify their resilience (Pedone et al., 2021; Gijzel et al., 2019; Whitson et al., 2016). Physiological, psychological, and social characteristics of older adults can influence the sustenance of resilience. In the face of growing health demands, family conflicts, financial instabilities, and societal role obscurities, psychological vigor is vital to reduce the likelihood of complications (Laird et al., 2019; Kok et al., 2018). Psychological resilience substantially contributes to the predictive efficacy of older adults to meet the challenges of the aging process (Kim et al., 2021; Taylor & Carr, 2021). While coping in its sense is encouraging, societal encouragement and the availability of support systems for older adults are vital (Carandang et al., 2020). The critical role of social engagement of older adults has been instrumental in successful aging due to societal commitment, heightened self-worth, and various opportunities for interest and socialization (Moore et al., 2015).

As a process, resilience involves acceptance of age-related changes. The ability to respond to these challenges provides an overview of how older adults can spring back from these adversities. Through individually appropriate strategies and available resources, older adults can adaptively cope with various difficulties. Manifested by a positive outlook and coping, resiliency among older adults translates into a practice of identifying strengths that can be used as assets, and acknowledging weaknesses, as a starting point for assistance.

Conclusion

Synthesis

Resiliency is when the older adult's initiative to institute measures is aligned with an outlook to recover positively from challenging life events of aging. Internally and externally motivated, stressors initiate adaptation whereas resilience, as an intricate process results in older adults' utilization of appropriate strategies and resources for successful aging.

Recommendations for Further Studies

As a concept, resilience can be understood as a variable in studies that associates with successful aging, burden, and quality of life. While it has been poorly addressed as a process that develops among individuals, the authors recommend that future studies should examine its conception and development. Understanding this aspect can pave the way for a wide

perspective of resilience translated into the practice of the care of older adults with varying levels of adaptive coping.

The authors of this paper aspire that this paper has contributed to the view of resiliency, as a process that is relevant to determining how older adults cope with a positive outlook in life.

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Unifying Role of Acceptance in the Trajectory Phases of Family Caregiving in the Care of Older Adults

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Abstract

Introduction. The living options for older adults in communities from various nations differ in several ways. Established by closed family ties, many older adults prefer to stay in their homes as they age, and this seems to be more ubiquitous than residential, retirement, or care homes for some cultures. From debt of gratitude to familial commitment, cultural expectation, and other related factors of caregiving capabilities, the unifying role of acceptance of assuming such responsibility has been poorly emphasized in the health of both older adults and family members across a trajectory. **Objective.** This academic paper article synthesizes related studies on the caregiving process, its recipient, provider, consequences, and resources threaded in the unifying role of acceptance towards the path to the successful delivery of quality and individualized care needs of older adults. **Findings.** It highlights the view of acceptance as an integral factor in the initiation, assumption, and termination of the care process from the varying degree of the cultural influence of this so-called intergenerational family solidarity. It reinforces the idea of role acceptance which is equivalent to the anticipation of consequences in different aspects. Finally, the findings illuminate the pivotal role of both intrinsic and external resources across phases of the family caregiving trajectory. **Conclusion.** Cultural diversity draws its concept of acceptance to caregiving of older adults and acceptance holds true to the context of living with them in their respective households with relevant issues such as societal obligation, fear of embarrassment, and an opportunity to find meaning in these caring experiences. **Recommendations.** Future studies that examine the critical purpose of acceptance in disease-specific contexts, caregiving self-efficacy, caregiver burden, and resource availability are proposed.

Keywords : acceptance, aged, caregivers, cultural diversity, family, self-efficacy

Introduction

The rapidly aging population translates into a societal decline in productivity and economic prosperity owing to the changes in the patterns of work and retirement and the complex health needs of older adults. In the face of physical dependency and cognitive decline, it is inherent for families to watch over their older adults, and this has been endured through generations (Schulz et al., 2020; Paguirigan, 2019). Family caregiving of older adults is described when a family member, mostly an informal care provider delivers a variety of supportive services, especially with activities of daily living in a person's home spanned for relatively long periods (Or & Kartal, 2019; Trettetteig et al., 2017). This practice is widely witnessed as around 85% to 95% of older adults accept care from their families worldwide (Luichies et al., 2020; Gaugler et al., 2018). Endured through several generations, caring as a practice reflects an agreement of both the family members and their older adults to be enclosed in a caregiving relationship with an implied acceptance of the situation.

Acceptance is exemplified when a person consents to take something that is offered. Within a ubiquitous implementation of family caregiving, acceptance of the role spans several considerations that encompass the influence of culture, debt of gratitude, societal expectation, familial commitment, and resource availability (Feliciano et al., 2020; Schulz et

al., 2020; Thomas et al., 2017). While acceptance is perceived to be a crucial role in role preparedness and execution, it is an underlying concept that is inherent to influence not only the initial phases of the caregiving process but the entirety of it boils down to this very concept. As both a pathway and a process, the caregiving trajectory illustrates how both parties go through sequential phases of role awareness, emerging responsibilities, growing care requirements, and end of life (Feliciano et al., 2022; Schulz & Eden, 2016). Within these phases, acceptance is integral as it affects the process in its entirety, and it compromises the health of both older adults and family caregivers.

Understanding acceptance in the context of family members who expect future caregiving roles of their older adults with various health care demands emanating from disease-specific, physically, and cognitively impairing conditions is vital in ensuring that quality and individualized care is delivered appropriately while maintaining an optimal level of physical, mental, social, psychological, and spiritual wellness on the part of the caregiver. For a successful caring process to ensue, resources can contribute to adequate preparedness, heightened caregiving self-efficacy, and reduced likelihood of caregiver burden (Feliciano et al., 2022; Sakakibara et al., 2015).

Imperative to this assimilation, the planned behavior of caring for family members should be based on the integration of acceptance, concretized through adequate preparedness, execution of evidence-based and individualized care services, reduced caregiver burden, and satisfying caring relationship. For acceptance to be evident, its underpinnings must be understood in the context of the caregiving trajectory of older adults. This academic paper aims to synthesize a review of the literature to deepen understanding of intergenerational family solidarity as a cohesive factor for acceptance, the process of acceptance and its implications, and the unifying role of acceptance and relevant resources in the trajectory phase of family caregiving in the care of older adults.

Findings

The unifying role of acceptance in the care of older adults is based on the anticipation of future older adult decline, the required assistance, and the consequences of adjustment and adaptation through the needed resources to sustain the process of caregiving. This section examines the multiple roles of caregivers and the impact on the health of both caregivers and their care recipients. Described as a complex and long-lasting process, family caregiving requires adequate preparation, and the embedded degree of role acceptance is crucial. Predominantly, this literature aims to highlight three (3) most essential concepts in the view of acceptance, as an integral factor for the caregiving process in the care of older adults ranging from cultural influence, the anticipation of decline and required caregiving roles, and the demand for resources in the trajectory of older adult care.

Intergenerational family solidarity as a cohesive factor for acceptance

Family psychology discusses the behavior of its members, and the quality of childrearing is crucial to understanding future care decisions of vulnerable members. As soon as they become responsible health decision-makers for their older adults, the degree of intergenerational relationship transforms it as enduring and consequential (Schulz et al., 2020; Thomas et al., 2017). Giving back the love and care they received as children establishes a connection of generations. This leads to a widespread cultural expectation of families to look after their older adults through a core concept of strong intergenerational family solidarity (Paguirigan, 2019). Global estimates suggested that 85% to 95% of older adults receive care from their families endured through several generations (Luichies et al., 2020; Gaugler et al., 2018). The conception of debt of gratitude transforms into a familial

obligation (Nguyen et al., 2021), a commitment, and an opportunity for finding meaning, especially at the end-of-life phase of family caregiving (Schulz & Eden, 2016). The cohesive factor for acceptance has cultural relevance and is concretized in societal acceptance of the practice to look after older adults by their own families (Revenson et al., 2016).

Acceptance of caregiving role and its consequences

The call for caregiving by families initiates when behavioral indications or changes in older adults' health significantly require intervention (Gilbert et al., 2018). Increasing reliance emanating from older adults' significant dependency precipitates domains of various care measures (Schulz et al., 2020). Allowing the family caregivers to acknowledge the change in family dynamics motivates them to adapt to circumstances (Nguyen & Levkoff, 2020). In the face of uncertainty about older adults' health, it is essential for the family members to process information and listen to concerns (Haji Assa & Umberger, 2022). The decision as to who accepts the role of caregiving is determined by existing relationships and geographical proximity (Scheibl et al. 2019; Solomon et al., 2018). While acceptance is demanded, the sudden decline of older adults' health proves to be challenging when compared to the gradual display of decline over time (Schulz & Eden, 2016).

Positive outcomes of caregiving are associated with favorable acceptance of the role which prepares the families to undertake challenging situations in older adult's life. Meanwhile, the consequences of family caregiving can be associated with long-lasting commitment with varying degrees of needed assistance, coordination with health care agencies in the face of one's own familial responsibilities, and social life (Kumagai, 2017; Thomas et al., 2017; Liu et al., 2020).

The burden of caregiving is a multidimensional concept that comprises social, emotional, and financial issues (Haji Assa & Umberger, 2022; Tamizi, et al., 2019). While there are several factors that have been implicated in the development of caregiver burden, older adults' and caregivers' characteristics play a role (Feliciano et al., 2022). For instance, older adults' degree of dependence is a constant predictor of caregiver burden due to the complexity of needs relating to ambulation, transfer, and toileting (Feliciano et al., 2022; Bekdemir & Ilhan, 2019). Regardless of the cause, the health of both caregivers and older adults is put into a compromise (Dawood, 2016; Rha et al., 2015; Sanaude & Boatemaa, 2015) which leads to diminished quality of life, decreased care provision, and deterioration of physical and psychological health (Lee et al., 2017; Liu et al., 2020).

Family caregiving trajectory and the resources required to sustain the process

Over time, the increasing complexity of older adult health discusses the implication of serious health consequences on the part of the caregiver due to an imbalance of available and required resources. The process that involves a series of phases that both older adults and their caregivers go through is described as a trajectory where demand for resources, confronting sudden or gradual older adult health decline, and end-of-life, roles, and challenges are all threaded (Schulz & Eden, 2016).

Limited care providers result in the utilization of available family members who are willing to assume roles (Harvath et al., 2020). Family members' self-efficacy is an essential intrinsic resource that capacitates them to act in accordance with desired health goals. Removing negative thoughts of caregiving consistently reduces feelings of burden (Grano et al., 2017). Greater self-efficacy requires understanding both the positive and negative aspects of caregiving (Liu et al., 2020) and this has been shown to allow confident decisions without the fear of negative consequences for older adults (Feliciano et al., 2022).

The primary domain of caregiving is related to medical care and the family caregivers act as an information source during clinical appointments (Assa et al., 2021; Krutter et al., 2020). Arrangements can be made to the caregiver to allow for flexibility and friendly guidelines to allow them to cope with the stressful impact of caregiving (Bell et al., 2019). In various periods, caregivers' needs must be monitored and addressed in the face of highly stressful events such as older adults' emergent admission to hospitals, discharge from hospital to home, or transfer to another facility (Gitlin, 2019; Jehangir et al., 2019; Schulz & Eden, 2016). Family engagement and other means of social support are likely to contribute to decreasing the caregiver burden (Assa et al., 2021). Resources come from various forms and are integral in the meaningful care of older adults in the face of co-morbidities, physical dependency, and required hospitalization. Financial support and improvement of self-efficacy are significant predictors to lower caregiver burden (Feliciano et al., 2022).

Conclusion

Synthesis

Acceptance, broadly defined as consenting to receive or undertake something that is offered is threaded in a multi-dimensional context of personal, socio-economic, cultural, psychological, and spiritual aspects of family caregiving responsibilities endured and demanded by a significant amount of energy, time, self-efficacy, and resources. While the concept of family caregiving holds true in some nations, cultural diversity paves the way for the acceptance of the institutionalization of older adult care in facilities, which provides gaps and entertains future research works on this conception. Similarly, the underlying context of acceptance in the assumption of caregiving roles must be seen in the light of physical and cognitive decline exemplified in specific health alterations in both acute and chronic duration.

Recommendations for Further Studies

From a vast array of cultural influences on the conception of debt of gratitude and family caregiving in respective households versus the widely accepted furtherance in the future care of family older adults in nursing homes, much is needed to examine the underlying contextual and operational definitions of acceptance in this field of gerontology. Additionally, future research studies must examine the relative influence of levels of acceptance on caregiver burden with consideration of role preparedness, resource availability, caregiving self-efficacy, and witness of end-of-life care to older adults. The authors of this paper hope that this paper has contributed to the much widely witnessed practice of family caregiving of older adults despite the little emphasis in the literature on the acceptance level of family members and its impact on the health of both care recipient and giver.

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Nursing Educators Technological Competency: Perceptions and Experiences in Theoretical Pedagogy and Praxis

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Abstract

Technology now serves as the medium for teaching nursing students, who, in the future, are bound to work in the healthcare industry. This abrupt shift in the educational sector necessitates nursing faculty instructors to be technologically competent. An absence of specialized mastery and innovative comprehension represents a test of the nature of well-being administrations and conceivably to security, nobility, and, patients satisfaction. Moreover, their perception and experience towards technology could also affect their competency with technological use. The aim of this academic paper synthesizes related studies on the technological competencies of nursing educators on how they apply these changes in teaching pedagogy and clinical practice throughout their educational programs. Several nurse educators are competent in utilizing pedagogical outcomes managed by technological advancements had a positive perspective on how this modernization could be advantageous in nursing education and praxis. Notwithstanding, various papers suggested that innovation could exclusively be used for digitalization as opposed to being educationally ideal. The series of innovation in the academe ought to be executed all through the educational plan to guarantee understudies' abilities and capacity in innovation for them to perform tasks and impart really. Therefore, the teachers' ability to adopt and competently utilize technology are important considerations when implementing innovations in the education settings. Instructors must have the option to involve computerized innovation in academically significant ways to help understudy learning and, ought to show fundamental advanced abilities to future experts how the development of the intervention program can help sustain the nursing faculties technological skills, improve their teaching methods, and allow positive learning experiences for the students even in a virtual environment

Keywords : Competency, Curriculum, Digital Technology, Faculty, Nursing, Perceptions

Introduction

The turn of events and progression in the usage of innovation in medical care straightforwardly sway the nursing profession and, nursing education. The pandemic has brought the mandatory shifting of pedagogy into digital platforms, especially in nursing education (Singh et al., 2021). Online teaching has suddenly become the primary mode of facilitating medical education, a format that may be utilized as long as the pandemic continues (Motte-Signoret et al., 2021). The way that the methods of instruction being given by the colleges and universities are turning out to be perpetually digitized has resulted in the emergence of difficulties for some college instructors specifically in terms of giving excellent quality of education and adjusting to the requirements of the changing academic instructions. The usage of innovation, the digitalization of learning conditions, and the rising pervasiveness of distance learning expect teachers to be skilled in advanced teaching method in digital pedagogy (From, 2017).

Moreover, a more significant level of skill in computerized teaching methods is required for instructors to address the difficulty of teaching future experts who themselves are profoundly carefully equipped (Ryhtä, 2020).

Technology conveys the capability of upgrading the quality, wellbeing, and proficiency of medical care administrations, and technological literacy contributes to obtaining the knowledge and understanding of the significant role that technology holds in healthcare services (Gonen et al., 2016). Many nations have ceased face-to-face learning afterward and a majority of the higher education systems work through e-learning, wherein technology is deemed as the primary medium for instructors to deliver and teach the learning materials to their students (Azzi-Huck & Shmis, 2020). Stakeholders are now reevaluating how to best use web-based learning (Jowsey et al., 2020), and educators in like manner have a potential chance to return to the fundamental presumptions around how they show and how students learn in the advent of modernization.

Advanced skill is the capacity to make and utilize a specific area of innovation, which is acquired through broad trial and error and learning in its exploration, improvement, and work underway. Nurse educators must contemplate strategies for leading the new generation of nursing students to be in line with the current trends which should reflect constantly on the essence and goals of the nursing education (Cheng, 2021). This relates to the educators' abilities and pre-existing information on the digital devices and applications being utilized in their pedagogy. Although most of these studies discuss whether or not faculty are technologically competent, gaps and insufficiency in discussing the readiness of nursing educators alongside their capacity to get to innovative assets, and the viewpoint of the workforce on using innovations for distance learning instructions have still arisen (Marek et al., 2021). While it is essential that nurse educators continue to publish a mechanism for open discussion and showcase transparency in our teaching and learning approaches, educators should continuously scrutinize and devise plans and strategies for leading the new generation of nursing students to be in line with current trends (Cheng, 2021; Smart et al., 2020). We need a higher level of shreds of proof to reinforce the argument that innovation further develops learners' outputs which in this manner accentuates the significance of advanced importance of digital competence involving professional knowledge and skills and its positive effect on clinical settings and patient level of care (Meum et al., 2021; Smart et al., 2020).

Technological Competency

It is of focal significance that innovation is executed both in the theoretical pedagogy and praxis of health personnel to guarantee and keep up with undeniable level of proficient capabilities. Nursing schools is recommended to be a source for long-lasting learning, and training understudies to be proactive and basic concerning innovative advances that are focused on nursing education (Nes et al., 2021).

Technological competence is the ability to create and use a particular field of technology effectively, which is gained through extensive experimentation and learning in its research, development, and employment in its production (Locsin, 2017). Nursing students need technological literacy to become proficient, and competent (Nes et al., 2021) for them to simultaneously foster their ability to perform decisive reasoning that is associated with the use of technology in education and their profession (Raman, 2015). Nursing educators now must be well-equipped with the skills and knowledge in technology and should know how to operate and troubleshoot digital devices and applications to make complex education ideas accessible to experienced co-educators and clinicians (Weeks et al., 2019).

The viewpoints of the faculty regarding online education are an important aspect when addressing concerns (Farhan et al., 2019). Also, the voices or support of the faculty are needed to embrace the new educational technology (Naseem 2019), which in fruition, will

contribute to the achievement of attaining successful e-learning systems in academic organizations (Elsahmi et al., 2018). To meet student demand for online learning, educational institutions must increasingly provide students with flexible learning environments (Ortega-Morán et al., 2020).

Nurse educators as well as practitioners and students will need to cultivate strategies when dealing with the enormous amount of new data, concepts, and skills related to technological development (Nes et al., 2021). Online education requires teachers to improve their competency in three major areas; pedagogy, technology, and content knowledge (Nimavat et al., 2021). In an online setting, faculty members may find it difficult to interact with their students; it appears that most of the learning activities that involve interprofessional team interaction results in positive changes in student perceptions and attitudes (Fox et al., 2018) or anticipate promoting their learning and development.

Educators need to become aware of who the students are, the things they need to learn, the approach on how to effectively teach them, and the skills they need to master remains a challenge to instructional staff in higher education because they have to keep pace with the technological innovations and approaches being used for teaching and learning in an online setting.

Perceptions towards e-Learning

In the event of the sudden emergence of the pandemic, the delivery of education to students still perseveres which has made the institutions engage in e-learning platforms (Alsoufi et al., 2020). However, following this, a key factor to consider when understanding how to proceed with e-learning effectively is to understand teachers' perception of e-learning (Parte et al., 2021). Most faculty members indicated that online class preparations require additional effort to ensure online courses are successful and interactive. For most teachers, this extra effort can be challenging and can result in a negative perception of online learning (Almahasees et al., 2021).

Educational advancements on instruction were perceived as an innovative method in teaching, with the most preponderant element being related to the usual form of practice, a situation in which games were the most significant predictors to invigorate and stimulate the students' learning (Gadelha et al., 2019). Perception can significantly impact how one proceeds with their engagement in e-learning and can influence the efficacy of one's work. Educators who are competent in digital pedagogy can integrate digital technology into education and can teach the essential digital skills students need in the working and professional setup (Smart et al., 2020).

However, the educators were concerned that technology might solely be utilized for the sake of digitalization instead of being pedagogically preferable (Ryhtä et al., 2020). It has been recognized, that instructors need the competence in creating digital pedagogy (Webb et al., 2018). On the contrary, several studies display the overall competence of nurse educators (Salmien et al., 2021; Tuomikoski et al., 2020; Kasam et al., 2107) be that as it may, has been an inadequate spotlight on their capability in the computerized instructional method. Analyzing the perceptions of the nurse instructors permits us to get the peculiarities according to the teachers' perspectives. This information can be used in fostering an instrument for measuring competence levels in digital pedagogy.

Experiences towards e-Learning

The increased usage of digital technology impacts each aspect of society. It opens up new possibilities for fulfilling various demands and issues (Al-Salman et al., 2021). The implementation of information technology in healthcare settings promotes aspects such as patient safety, evidence-based nursing care (Abdrbo, 2015), strategic needs, professional growth, and technological capabilities that have influenced the design and development of digital technologies in higher education (Sormunen et al., 2021). The use of digital technology has been identified as one of the critical proficiencies for continuous learning in a global and domestic initiative (Van Laar et al., 2020). Blending technology into education is a critical priority for educators, particularly in this day and age where technology has gained immense importance in our lives and professions (Adel et al., 2021). Teachers have an essential role to their students in making learning engaging while molding their attitudes, developing better personalities, and most significantly assisting students to complete the learning pedagogies. These unprecedented times compelled the change to online learning (Suliman et al., 2021).

Experiencing challenges that were focused on adapting to online teaching offers different experiences for educators (Estrellan et al., 2021), burdens, burnout; the need for social and technical support, and the shortage of online learning in fulfilling the educational outcomes of clinical courses are some of the challenges being faced by teachers (Suliman et al., 2021). Some educators could acclimate quite adequately, others have difficulty adjusting. One of the highest challenges for accepting e-learning was insufficient or unstable internet connectivity, inadequate computer laboratories, lack of computers or devices, and technical problems (Zalat et al., 2021). The lack of technological competency or preparedness for the shift in teaching methods can significantly influence teachers' experiences regarding e-learning (Nimavat et el., 2021).

On the other side of the spectrum, this unprecedented time has stimulated the growth of online educational activities so that there would be no interruption to education, and many nurse educators have been involved in how to best offer online course material, that involves students' participation, and perform practice evaluations (Jaffar et al., 2022). The teacher's constant consultation and the exchange of summaries using electronic resources have set the standard in self-education that promoted distance education program goal, to meet the students' educational needs effectively (Meniailo et al., 2021). In distance learning, the student's primary role, in general, is to learn, which requires a high level of motivation and self-organization because, as previously stated, distance learning is primarily about self-education or the student's ability to work independently (Kovbasnyuk & Styfanyshyn, 2020).

Additionally, digitally competent educators are able to manage the use of technology in teaching, and learning and, can also assess their students' knowledge using digital technology (Redecker, 2019; Van Laar et al., 2017; Webb et al., 2017). The usage of computerized innovation in learning settings has been recognized to enjoy many benefits, and instructors opted to use advanced innovation in adaptable and receptive ways (McDonald et al., 2018; Webb et al., 2017; Gonen et al., 2016). Such experiences have shaped the image educators and faculty have in online classes. While professors understand that digital learning is the only viable option during the pandemic to continue education, the overall experience can be either negative or positive, depending on the teachers' preparedness and technological competence.

The technological competence of the nurse educators encompasses resilience to changes and willingness to adapt to these changes. Healthcare professionals need the motivation and willingness to acquire experience of digitalization in their professional

context (Konttila et al., 2019). Health informatics is essential in all core competencies in nursing; the academe and its organizational support appear to be an essential factor for building positive experiences of digitalization of healthcare professionals (Anderberg et al., 2019; Konttila et al., 2019). From an educator's perspective, it is of great importance that students are prepared for the new demands and needs of the patients and, educators should not be limited by current praxis paradigms (Anderberg et al., 2019), of the pedagogical framework which could yield a positive outcome in the baccalaureate nursing education (Youhasan et al., 2021).

Conclusion

Synthesis

Studies that carry the innovative capabilities to a more significant level are required, including critical thinking and decisive reasoning. The integration of technology in nursing education be executed all through the educational plan to guarantee that the learners' abilities and capacity to perform tasks and discuss in line with present innovation and advancmenets. Therefore, the teachers' ability to adopt and competently utilize technology are important considerations when implementing innovations in the education settings. This suggests that there is a need to improve the technical competency of the nursing faculty members in some aspects and to a certain extent or degree. In addition to this, their concerns must also be acknowledged appropriately to enhance their teaching practices and technology use. Moreover, with the increased demand for online education due to the uncertainty of time, nursing educators must be able to effectively integrate online technology within the pedagogy and clinical praxis for the continuous learning process by the student nurses thru digitalization. It also highlighted that the concerns about technology use must be acknowledged and resolved appropriately by higher educational institutions. Later on, the aftereffects of this study can be used as the basis for the development of an instrument to assess the degree of capability in digital pedagogy and practice of nursing educators. Looking at the viewpoint of the teachers will permit us to get better peculiarities according to the instructors' perspective.

Recommendations for Further Studies

The educators should be able to integrate advanced innovations in academically significant ways to help the learners academically and to further strength fundamentally technological abilities to in their professional development. A development of an intervention program could help sustain the nursing faculty's technological skills, improve their teaching methods, and allow positive learning experiences for the students even in a virtual environment. Hence, to ensure the program's effectiveness, a comprehensive assessment and implementation must be done accordingly. One of the strengths of the research article is that it is timely and relevant to the "new normal" of instructions which could contribute to the scaffolding of an instrument that could measure the technical competence in digital pedagogy and praxis of educators in nursing profession.

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The Filipino Nurse: A Caregiver Beyond Borders

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Abstract

Introduction. The Philippines is recognized as a major source of health care workers globally despite experiencing its own lack of nurses. Filipino are recruited in different developed countries due to the global shortage of nurses and despite being family-oriented, they choose to leave their loved ones to provide services to other nations. Using various literature, this paper seeks to further understand the experiences of Filipino nurses which includes the motivating factors that led to their decision to become expatriate nurses, their experiences in caring for patients in other countries and the impact of their decision to the Philippines. **Findings.** Three (3) vital concepts are highlighted in this paper: (a) Motivating factors that lead to Filipino nurses working abroad include the desire to support the family, the compensation received abroad, and the influence of peers, co-workers, and working conditions. (b)Migrant workers experience more challenges than local workers due to different factors such as communication issues, differences in nursing roles in the working environment, and work discrimination. (c)Migration impacts the Philippines in various ways. Economy benefits because of the remittances coming from the host countries. However, it is imperative to manage migration responsibly to avoid a shortage of nurses. **Conclusion.** Migrant Filipino nurses primarily work abroad to provide better support to their families in the Philippines. Despite the challenges experienced they continue to provide service globally which impacts the Philippines as well. **Recommendations.** Future studies that are country-specific and/or focused on the coping mechanisms to deal with challenges abroad are recommended.

Keywords : expatriate nurse, Filipino nurse, migration, nurses abroad

Introduction

The global shortage of nurses is expected to increase to 7.6 million by 2030, which is expected to be highest in middle- and high-income countries (Lieu et al., 2016), and the Philippines has been recognized as the largest exporter of nurses globally (Baker, 2020). It has been producing nurses who decide to leave their homeland and render care to the citizens from other countries such as the United States, the United Kingdom, and the Middle East. These economically advantaged countries, especially those in the global north, rely on the active recruitment of expatriate nurses from developing countries in the global south, such as the Philippines, to solve the need to suffice their lack of nurses (Bautista et al.,2019; Drennan & Ross, 2019).

Foreign-educated health care professionals comprise most of the medical and nursing workforce in developing countries, with the majority coming from the Philippines (Kingma, 2018). This may be since the Philippines has a bilateral agreement with more than 20 countries and was able to export over 92,000 nurses from 2000 to 2017 (Philippine Statistics Authority, 2017).

However, scarcity of nurses in the Philippines was reported due to the sheer number of health care providers leaving the country and the extension of the 10-year basic education to 12 years where two additional years in high school were experienced. As the Philippines exports nurses, only a few are left to serve the country (Cuevas et., al, 2021).

This academic paper integrates various literature that will aid in further understanding the experiences of Filipino migrant nurses or expatriate nurses: how they derived the decision of going abroad, what were the challenges, and what impact did they bring to the Philippines.

Findings

This academic paper highlights three (3) vital concepts regarding the experience of Filipino migrant nurses. This section explores the motivating factors that made Filipino nurses decide to leave the country and work elsewhere, the challenges and experiences of Filipino nurses working in a host country, and the impact of migration to the Philippines.

Motivating Filipino nurses to leave their country: the passion, the compensation, and the influence

Passion in this context refers to the Filipino nurses' love for their families. Migration is closely related to family duty, and it has become a rite of passage that represents success, especially for nurses. Filipinos are family-oriented and would sacrifice for their families. (Smith & Gillin, 2021). Studies have yielded that pursuing nursing education to become a professional nurse is often made by the family to secure migratory opportunities (Ortiga, 2020).

Filipino nurses started studying the profession with a mindset to leave the Philippines and work in other countries (Cuevas et., al, 2021). Although it is primarily due to the numerous job opportunities offered outside of their homeland, such a mindset may also be attributed to the existence of "migration institutions" such as nursing schools oriented toward the global nursing market (Ortiga, 2014). In the end, it provides Filipino nurses with a feeling of security in terms of providing a good future for their soon-to-be families (Cuevas et., al, 2021). This also considers the compensation.

In line with the compensation, the US Bureau of Labor Statistics reported that in March 2018, the median salary of registered nurses per year from May 2016 to May 2017 is USD70,000.00 or PHP3,770,000.00. This is more than tenfold what a Filipino nurse would expect to receive yearly in the Philippines. The Philippine Nursing Act of 2002 says that nurses working in the Philippines should be receiving PHP30,53.00 monthly, or around PHP366,000.00 per year. Unfortunately, this is not the case for most nurses since they receive a lower amount for their salaries. Poor working conditions, including low salaries, extended shifts, and scarcity of opportunity for professional development are the major reasons for Filipino nurses to seek employment outside of the country.

However, it should also be noted that the Filipino nurses still felt a certain kind of joy caring for their fellowmen in the Philippines. It was for this reason, that aside from the required years of experience to work abroad, some of the nurses provided service to the Philippines before their deployment to other countries. This was also accompanied by the feeling of responsibility in supporting their parents who worked for their education. Other migrant nurses would bring their parents to the country where they work to take care of their children or to have a better life (Cuevas et., al, 2021).

Lastly, Filipino nurses were influenced by their co-workers for overseas employment. Despite the working conditions of nurses in the Philippines, some were initially hesitant to leave their families and loved ones. However, they were persuaded to join their peers during application processing (Cuevas et al., 2021). On the other hand, those nurses who were perceiving that they were given little respect by the government, by doctors, or by patients, and that clinical hierarchies were also evident in the Philippines were immediately influenced by work in other countries (Smith and Gillin 2021).

Holding on to the decision. Embracing the choice despite the challenges

Stressors in healthcare are constant, but migrant nurses experience even greater challenges since they encounter additional stressors such as adaptation issues, language barriers, and discrimination (Connor, 2016). Those who had the intention to migrate were more likely to meet the criterion for having the symptoms of depression and were found to have a higher score for general perceived stress (de Castro et al., 2014).

Migrant nurses developed various coping mechanisms to deal with the challenges of working in another country. Different themes were identified that reflected similar coping behaviors for each. For example, Filipino nurses manifested coping behaviors related to their passion for supporting their families. They would communicate with their loved ones in the Philippines using the available technology to alleviate loneliness (Okouhga & Tilki, 2015).

Communication was a concern for many expatriate nurses. Despite being educated in English, the language became a barrier to providing quality service. This is due to the difference in the accent and the use of the English language in the host country (Montayre et al., 2017). Nurses also needed to adjust to a less formal society which has a more relaxed working environment than in their home country. For example, co-workers call each other on a first-name basis. In the Philippines, one would only call another via the first name if they are relatives or are close friends. They were also surprised by how the family members in the foreign country where they were working communicated with relatives, who the Filipino nurses care for. Instead of visiting the patient, relatives would only call and ask about the patient. (Okouhga & Tilki, 2015).

Differences in autonomous decision-making in the field of nursing were noted. Some host countries have migrant nurses who had less autonomy as compared to other countries like Canada, where there was increased responsibility of nurses as decision-makers and were more autonomous. With such, Filipino nurses experienced a great difference in the work system as well as the nursing roles in the host countries. Work-related difficulties were therefore reported to be experienced by Filipino nurses due to the difference in terms of organization of work and routine nurses do in the host countries. (Montayre et al., 2017).

They would seek social support from fellow expatriate nurses. They connected with people with similar experiences and backgrounds, especially with fellow Filipinos. Many found comfort in just knowing that there were other Filipinos in their workplace. Some Filipino migrant nurses encountered unfair working practices and discrimination. They handled such by working harder to prove themselves. (Connor, 2016).

Despite the challenges experienced by Filipino nurses; the Philippines continued to be a major source country of foreign-educated nurses in the global market.

The impact of nurse migration to the Philippines

As a leading country in supplying trained nurses globally, the Philippines had an increased number of nurses being sent to other countries. This was a challenge since responsible management of migration was imperative to retain health workers (Thompson & Walton-Roberts, 2018). The economic benefits of nurses migrating from the Philippines to other countries have been reported. In a broader sense, the Philippines produce nurses for export to draw remittances from other countries. Remittances are considered a major source of income in the Philippines (Marcus et al., 2014).

The Philippine government attempted to balance concerns about the economic roles of migrant nurses and their rights as migrants. However, the economic importance of migrant nurses was evident as policy decisions favored economic concerns (Masselink & Daniel, 2013).

However, there is a negative impact on nurse emigration from "developing" countries. It was reported in terms of the resources invested in the training of health workers, only to see them leave and provide services to other countries (Allutis et al., 2014).

It has been discussed that the potential of national governments to ensure that global frameworks for development, such as the Sustainable Development Goals, are met has been limited by the very nature of migration of health workers (Holliday et al., 2018.) However, policies were placed to ensure and promote opportunities for return and circular migration which increased skills transfer among nurses from various countries (Vartiainen et al,2016).

In fact, during the coronavirus disease 2019 (Covid-19) pandemic, the Philippine government suspended the deployment of health workers overseas. During the state of a public health emergency, this was to ensure that the Philippines maintains an adequate health care workforce. Governing Board Resolution No. 09, series of 2020 temporarily suspended sending Filipino health care workers, especially nurses, abroad until the crisis is over (DOLE, 2020).

Conclusion

Synthesis

Filipino nurses are recognized quality healthcare workers. However, several factors contribute to the decision of Filipino nurses to leave their families and work abroad. A concrete reason is to seek greener pasture not only for themselves but more importantly, for their families. The current salary scale offered in the Philippines is much less compared to the compensation offered abroad. Nurses are also influenced to migrate by their peers and co-workers or by the working conditions they experience in the country.

Once working abroad, Filipino nurses experience challenges that are primarily due to the difference in the working environment between the Philippines and their host country. Coping mechanisms were observed and Filipino nurses continue to provide services globally despite the challenges.

This provision of international health care service impacts the Philippines. Economically, the remittances coming from the migrant nurses are a major source of income for the country. However, responsible management of migration is imperative to avoid experiencing a lack of nurses, which was felt during the COVID-19 pandemic.

Recommendations for Further Studies

The authors of this academic paper hope that this has provided a wide array of evidence that would yield valuable information on the experiences of Filipino migrant nurses. With the varying cultures and lifestyles in every country, the authors recommend studies that describe the experiences of Filipino migrant nurses in a specific locale or region. This will be beneficial both for the Philippines and the host country since it may lead to the improvement of the working conditions in the health care setting. More information regarding the coping mechanisms utilized by Filipino nurses in dealing with stressors while working abroad is also encouraged to better understand their experience. It could also become a basis for policies, training, and self-development about deployment to other countries.

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The Influence of Empowerment on Nurses' Engagement, Satisfaction, Intent to stay and Workforce During Covid-19 Pandemic Era

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Abstract

Introduction. Workplace empowerment is critical for establishing a positive nursing work environment during nursing shortages. Improving nursing working conditions is vital to sustaining the workforce and the retention of nurses in the Profession. **Objectives.** The aims of this academic paper is to synthesize related studies on workplace empowerment relevant to improving nursing working conditions that are beneficial to the nursing administration in directing leaders' tactics for creating and maintaining an empowered work environment that will decrease nursing turnover intentions. Empowerment is seen as an effectual approach to further nurses' engagement, leading to job satisfaction among nurses. Intention to stay in the Profession is also associated with organizational culture, leadership style, and employee empowerment practices. The psychologically empowered nurse's premium satisfaction in the organization, thereby retaining them in the workplace. And When nurse managers and leaders foster an environment that supports and encourages nurses to take control of their own practice, nurses experience a higher degree of autonomy. **Conclusion.** the literature clearly defined the influence of empowerment on maintaining job engagement, increasing job satisfaction among nurses, decreasing turnover, and increasing job autonomy among nurses. These factors are critical in the nursing profession and premium positive outcomes in the organization. **Recommendations.** We recommend that future studies focus on nurse empowerment to increase the workforce. Such research would allow for the investigation of the impact of various healthcare systems, organizational structures, and policies on nurses' structural and psychological empowerment.

Keywords : empowerment, job satisfaction, nurse administrators, nurse turnovers, work engagement

Introduction

Nursing continues to be understaffed due to high turnover and unbalanced workload distribution. Numerous causes contribute to and are concerning the nurse shortage (Hu et al., 2022). However, this shortage is not just a nursing issue, and it requires collaborative efforts by nursing practice and education leaders, healthcare leaders, the government, and the media (ANA, 2021). Additionally, nursing workforce empowerment contributes to positive outcomes such as job satisfaction and intent to stay in the Profession.

Nurses play a significant role in today's quickly changing healthcare environment, described by quality patient care, workplace empowerment, and nursing shortages. Empowerment is defined as conferring on individuals the authority, responsibility, and freedom to act on their knowledge and instill their belief and confidence in their abilities to achieve and succeed (Choi et al., 2017; Laschinger & Fida, 2015). In Hadddad et al. (2022), the COVID-19 pandemic adds to the nursing workforce's ongoing professional burdens or stressors, putting them under pressure and impairing their performance and the quality of patient care. Persistent work stressors negatively affect the psychological well-being of nurses, resulting in burnout, which leads to dissatisfaction and nurse turnover. In Labrague et al. (2020), nurses' psychological stress, job burnout, and dissatisfaction resulted in higher turnover intentions. Therefore, it is essential to increase the retention rate of nurses and

ensure the quality of continuous nursing care, systematic measures to reduce stress and burnout, and increase nurses' satisfaction with their work. Thus, Empowering employees is a management strategy that has been demonstrated to be effective in fostering favorable work conditions within organizations.

Workplace empowerment is critical for establishing a positive nursing work environment during nursing shortages (Marin-Garcia & Bonavia, 2021). Moreover, improving nursing working conditions is vital to sustaining the workforce and the retention of nurses in the profession. Therefore, organizations must persist in searching for strategies to support staff nurses in creating a safe and empowering workplace while still providing high-quality patient care. Thus, this academic paper aims to synthesize related studies on workplace empowerment and its influence on work engagement, job satisfaction, intent to stay in the profession, and job autonomy relevant to improving nursing working conditions that are beneficial to the nursing administration in directing leaders' tactics for creating and maintaining an empowered work environment that will decrease nursing turnover intentions. This may result in increased nurse retention and favorable outcomes for the organization and its patients.

Empowerment influenced work engagement and job satisfaction

In Gong et al. (2020), the organization's perspective on empowerment implies that the workplace environment determines an individual's empowerment ability. Empowerment is seen as an effectual approach to further nurses' engagement, leading to job satisfaction among nurses. Findings suggest that psychologically empowered nurses may exhibit more work engagement, increasing job satisfaction, and emotional well-being. Work engagement benefits the organization by enhancing nursing performance, predicting patient satisfaction and reliability, and decreasing nurse turnover. In Labrague and de Los Santos (2021), organizational measures are crucial in increasing job satisfaction and reducing stress and burnout to address nurse retention and ensure the continuous provision of high-quality nursing care. This will lead to a lower incidence of intent to leave the organization and the Profession.

Leaders' empowering behavior has also been examined to explore work engagement and job satisfaction impacts. Nurses are expected to adapt to continual and rapid change in their work surroundings while adhering to all regulatory and practice standards. In Sulaiman et al. (2021) and Stamps et al. (2021), the amount of energy required to meet these expectations makes it difficult for staff nurses to maintain a continual level of engagement and commitment to their organization's employees. Therefore, leaders are critical in motivating staff and influencing staff nurses' work engagement and intent to stay in the organization to ensure great organizational and patient results. Furthermore, leaders should possess this empowering behavior to empower the nursing profession. Also, it is suggested that leaders include empowering behaviors to promote the psychological well-being of their staff and hence promote engagement and satisfaction. Thus, leaders support nursing staff through their challenges while maintaining quality patient care.

Nursing empowerment and their intent to stay in the Profession

In Berridge et al. (2020), worker empowerment was strongly connected with nursing assistant retention. Staff stability is also associated with organizational culture, leadership style, and employee empowerment practices. The study's findings support those initiatives to strengthen leadership and staff empowerment practices that may help retain staff. Engaging and committing staff to improving patient outcomes in a systematic interdisciplinary approach requires well-defined frameworks, procedures, and resources and a governance and

policy structure that makes results observable and held responsibly. In Amarneh et al. (2021), Psychological empowerment positively affects various work-related outcomes, including enhanced organizational commitment. The psychologically empowered nurse's premium satisfaction in the organization, thereby retaining them in the workplace.

Additionally, less satisfied staff with a high level of psychological empowerment will have a lower tendency to leave the organization (Amarneh et al., 2021). Nurses' positive empowerment will increase their workplace confidence and reduce turnover (Amarneh et al., 2021; Berridge et al., 2020). Healthcare organization should integrate their human resource strategies with their goals while keeping nurses satisfied. Organizational policies need to be enhanced to provide greater flexibility in implementing alternative methods to mitigate nursing turnovers and promote nurse retention.

Empowerment and Job Autonomy

In Gottlieb et al. (2021), the epidemic unintentionally reintroduced nurses to the public consciousness since their expertise and skills were in considerable demand. While it will take years to fully assess the impact of the Covid-19 pandemic on the nursing workforce, research indicates that many nurses have been traumatized by the tragedy and are seeking to leave the profession. When nurse managers and leaders foster an environment that promotes and supports nurses to take control of their own practice, nurses experience a higher degree of autonomy. Autonomy is the power to direct one's nursing practice. Leadership is essential in fostering conditions that permit nurses to express their autonomy and agency in the context of their profession. Thus, nurses will be satisfied with their jobs, influencing their decision to stay in their organization and career and, most importantly, improving patient safety and quality of care.

In Gebregziabher et al. (2020), when nurses are given more autonomy in their work environments, they are more likely to develop stronger critical thinking abilities and a more favorable psychological attitude toward leaving the firm. As a result of losing influence over their actions, they may have decreased job satisfaction, contributing to their willingness to remain with their organization. Nurse Managers should assess the structures in their organizations to identify barriers that prevent staff nurses from feeling secure in their jobs. They should also ensure there are empowering factors at work, give their employees access to organizational empowering structures to provide them with a greater sense of autonomy and influence at work, and use psychological empowerment to improve the image of nursing.

Conclusion

Synthesis

The academic paper clearly defined the influence of empowerment on maintaining job engagement, increasing job satisfaction among nurses, decreasing turnover, and increasing job autonomy among nurses. These factors are critical in the nursing profession and premium positive outcomes in the organization. Nurses must be innovative to give patients the best and safest care possible. It is necessary to have an empowered and engaged nursing workforce. Allowing job autonomy will help moderate burnout and the intent to leave the workforce. Numerous organizations have recognized and sought to achieve a high level of patient safety, quality, and satisfaction. At this point, investing in workplace empowerment is critical. It is vital for health care facilities to be able to care for the increasing number of patients. By investing in and enacting policies that support nursing practice, we can contribute to increasing the appeal of nursing as a profession.

Recommendations for Further Studies

We recommend that future studies focus on nurse empowerment and strategies to sustain the nursing workforce. Such research would investigate the impact of various healthcare systems, organizational structures, and policies on structural and psychological empowerment, including leaders' empowering behavior.

New research should be promoted since empowerment offers the instruments, resources, and environment for professional development and organizational success.

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Doing research at home: the potential of virtual screening of selected secondary plant metabolites in drug discovery

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Abstract

The COVID -19 pandemic may have caused a huge challenge in conducting scientific research in education systems that are massively relying on wet lab science approaches. Students taking up their final years are still obliged to carry over their thesis with the available resources and home-based approaches. This is where in-silico analyses (a technique that focuses primarily on computational mechanisms) come in handy in applying biological principles to health research. The study aims on providing a comprehensive methodology on how virtual screening is done by testing molecular interaction through docking simulations between ligands of *Blumea balsamifera* & *Momordica charantia* into COVID-19 receptor*; Pandanusphenol A* ligand into diabetes receptor, *&* ligand *Mappain* into a cancer-related receptor. Ligands were assessed to drug likeness, toxicity, hydrophilicity, and water solubility of the ligands. Results have revealed that the top-ranking phytochemicals include tormentic acid-methyl ester, ganoderic acid Y from M. charantia, and arnicolide D from B. balsamifera against SARS-CoV-2 spike RBD. On the other hand, it is predicted that pandanusphenol A has a higher affinity than acarbose to the given alpha-glucosidase enzymes; pharmacokinetic studies predict the molecule to be a brain-barrier permeant and a CYP2D6 inhibitor, insinuating that it might have neuromedical properties; it is also predicted to be nontoxic. Lastly, Mappain may act as an inhibitor to selected proteins related to cancer as it successfully bound with the selected cancer targets, while taking note of its lower binding affinity compared to standard drugs. This exploration can function as a complement to wet lab approaches which can aid in decision making, envisioning innovative thoughts, and offering solutions to problems that cannot be tested due to design difficulties and high expenditure.

Keywords : Molecular docking, in-silico, virtual screening, toxicity, Lipinski rule

1. Introduction

The current COVID-19 pandemic has caused the scientific community, especially the education system (Daniel, 2020) a huge challenge in terms of conducting health-related research (Saberi, 2020). The problem exists as universities were closed and most laboratory activities were shut down due to several lockdowns and restrictions, especially where COVID transmissions are high. The situation necessitates a type of research where students can still apply their acquired scientific principles into practice without the need to attend campus for laboratory work.

There is a growing demand for promising pharmacological targets for drug development (Meng et al., 2011) making it critical to find solutions or criteria that will quickly achieve the most feasible targets and compounds to make it to the clinic and then the market. One of the efforts that helped many experts in this matter is the emergence of computational methods, further aided by advances such as spectroscopy and crystallography. An example of this is in silico technique. Maia et al. (2020) described that with the use of in silico simulations, researchers have adopted the computer-aided drug design (CADD)

approach, which includes molecular modeling tools, to boost the usefulness of novel medications. Moreover, two types of CADD methods are ligand-based (LB) and structure-based (Yu & MacKerrel, 2016). In the past few years, Tao et al. (2019) said significant efforts regarding molecular modeling have arisen, including homology modeling, molecular dynamics, and molecular docking. Among these approaches, molecular docking became a prominent and most utilized method in structured-based design. Molecular docking became one of the most widely used computational approaches because of its ability to detect ligand-protein binding affinity and the architecture of the protein-ligand complex. This approach has been used for an extensive period, and it has resulted in the discovery and development of a large number of novel medications (Wang and Zhu, 2016).

Meng et al. (2011) suggest that an in silico molecular docking technique may be utilized to describe these atomic-level interactions between a small chemical and a protein. This method will allow researchers to distinguish the activities of minor compounds in the binding sites of target proteins and deduce basic biochemical processes. Dar & Mir (2017) also explained that the data gleaned through docking might be utilized to estimate the binding energy, free energy, and stabilization of complexes. The molecular docking approach is currently used to gauge the ligand-receptor complex's putative binding characteristics. The procedure consists of two main steps, namely (1) predicting the ligand structure as well as its location and orientation inside these sites (i.e., pose) and (2) determining the binding affinity (Meng et al., 2011). It is important to note that to conduct reliable docking experiments, a high-resolution X-ray, NMR, or homology-modeled structure of the biomolecule with a recognized or predicted binding site is demanded (Sethi et al., 2020).

Various laboratory types have emerged with the rise of scientific professions and research and a concerted attempt to make discoveries, each tailored to a particular use case. Regardless of the style, individuals concerned with science highly value laboratory experiences since they improve comprehension of the subject and promote critical thinking and scientific reasoning (Singer et al., 2006). Furthermore, the two categories are the dry and wet lab. A dry lab approach is where computational investigations are performed on a computer simulation to replicate a physical occurrence while wet lab approach chemicals, pharmaceuticals, or other biological molecules are controlled in liquid solutions or volatile phases (Chander, 2021).

Dry lab and wet lab approaches go hand in hand, according to a large body of literature. This occurrence has been seen in ongoing COVID-19 pharmacological research. For example, Bansal et al. (2021) did a study that included a dry lab, referring to in silico molecular docking. Their goal was to determine which pharmacologically active non-ribosomal peptides (NRPs) from marine microorganisms could suppress the virus's viral targets. Consequently, they performed docking of NRPs from marine microbes with S-glycoprotein and PLpro from SARS-CoV-2. According to Bansal et al. (2021), Gramicidin S is one of the medications with the most vigorous binding contact with target proteins. They further speculated that it could disrupt SARS spike protein binding to the human host ACE2 receptor, which indicated that it could prevent viral access into cells. Therefore, they concluded that more research is needed to prove Gramicidin's efficacy against COVID-19 infection. A year later, Enayathullah et al. (2022) conducted a study based on Bansal et al. (2021). However, they now included a wet lab in their investigation, notably RT-qPCR and MTT experiments. In their work, they also discovered that Gramicidin S has the potential to be developed as a medicinal chemical to alleviate COVID19. As a result, the work of Enayathullah et al. (2022) became consistent and confirmed the work of Bansal and colleagues.

2. Objectives

The study aims to give a comprehensive methodology on virtual screening while describing the molecular interactions between ligands of *Blumea balsamifera* & *Momordica charantia* into COVID-19 receptor*; Pandanusphenol A* ligand into diabetes receptor, & ligand *Mappain* into a cancer-related receptor. Additionally, the study will explore the drug-likeness of the secondary metabolites based on Lipinski's Rule of Five. It will also predict the toxicity (mutagenicity, tumorigenicity, irritant effect, reproductive toxicity), cLogP (hydrophilicity), and water solubility of the ligands.

3. Material and methods

For a comprehensive step-by-step procedure see Supplementary material (in https://drive.google.com/file/d/1CWcJi6105zMXynbVpHG0YAbxCgs5fPtO/view?usp=sharing)

Procurement of ligand and receptor protein files

The phytochemicals from the selected plants, as well as the positive control drugs, were obtained from the PubChem database. The 3D conformation of the ligands was then saved as an SDF file. One of the ligand molecules, pandanusphenol A, had its structure manually drawn using Avogadro (Avogadro version 1.2) in reference to the paper of Zhang et al., (2013). Lastly, all of the proteins conducted in the three studies were obtained from the Protein Data Bank and are saved as PDB files.

Preparation of ligands and receptors for molecular docking

The ligands were opened using Avogadro (v. 1.20) where energy minimization is performed for an optimal structure. Using AutoDock Tools and MGLTools (version 1.5.7) Gasteiger charges are added and they are saved as PDBQT files.

For the preparation of proteins, Biovia Discovery Studios (version 4.5) was used to remove water, co-crystallized ligands, and other bound residues. The protein files were then saved as PDB files and ran through PROCHECK (in https://saves.mbi.ucla.edu/) to confirm the stereochemical quality of the protein structure. Based on the Ramachandran plot, if the protein has at least 90% of its residues in favorable regions with no outlier residues, they are subject to docking. Proteins that do not pass the prior test are submitted to the YASARA Energy Minimization Server, wherein proteins are optimized by fixing the outlier residues and lowering their free energy. If outliers are still present, they are fixed through loop refinement using the program Modeller version 10.2. To improve the binding of the protein to ligands, polar hydrogens and Kollman charges were added to the structure using AutoDockTools-1.5.7.

Molecular Docking

Active sites were identified and the docking simulation was accomplished using AutoDock Vina using standard procedures. Nine docking poses were generated for each receptor-ligand complex, and the ones with the highest binding affinity (that is, lowest binding energy), were selected for the report. The 2D and 3D protein-ligand interactions were analyzed and visualized using Biovia Discovery Studios.

ADME and Toxicity prediction

Ligands were subjected to SwissADME (in http://www.swissadme.ch/index.php) to assess their drug-likeness based on Lipinski's Rule of Five. Using the same web tool, the BOILED-Egg model (brain or intestinal estimated permeation predictive model), was obtained to predict passive intestinal absorption and brain permeation of the ligands.

Lastly, OSIRIS Property Explorer was used to predict the toxicity (mutagenicity, tumorigenicity, irritant effect, reproductive toxicity), cLogP (hydrophilicity), and water solubility of the ligands.

4. Results

4.1. *Blumea balsamifera* and *Momordica charantia* phytochemicals *in silico analysis*

4.1.1. Molecular docking analysis

Eight phytochemicals from both *M. charantia* and *B. balsamifera*, with remdesivir as positive control, were docked against SARS-CoV-2 receptor binding protein (RBD)—i.e., RBD binding site is defined by polar Asn 501, Gln 409, Gln 493, Ser 494, Gln 498, Thr 415, as well as, charged Lys 417, Arg 403, Glu 406, Asp 405, Arg 408, finally, hydrophobic Tyr 453, Tyr 505, Phe497, Tyr 495, Leu 455, Phe 456 and Gly 416, Gly 496 amino acid residues (Chikhale et al., 2021). The binding affinities and interactions to the target protein of the phytochemicals, including remdesivir are listed in Figure 4.1.1; whereas the potential inhibitory mechanism of the ligands is illustrated in Figure 4.1.2; the druglikeness are listed on Figure 4.1.3; and the toxicities of the phytochemicals are noted on Figure 4.1.4.

Group	Cpd.	Binding Affinity with SARS-COV-2 RBD	Interacting residues: Hydrogen bonds	Interacting residues: Hydrophobic interactions
Phytochemicals from *M. charantia*	1	-6.1 kcal/mol	LYS 458 SER 459 ARG 466	None
	2	-6.5 kcal/mol	LYS 378 TYR 380 TYR 508	None
	3	-6.1 kcal/mol	ARG 403 TYR 453 GLY 496	None
	4	-6.4 kcal/mol	ASP 405	None
	5	-6.7 kcal/mol	LYS 378	None
Phytochemicals from *B. balsamifera*	6	-6.3 kcal/mol	SER 375 THR 376 ARG 408	None
	7	-5.4 kcal/mol	SER 371 LYS 378 PRO 384	None
	8	-5.7kcal/mol	THR 376	None
Positive control	9	-6.0 kcal/mol	TYR 453 GLY 496 GLN 498	ARG 403 TYR 449 TYR 505

Figure 4.1.1. Binding affinities and interactions of ligands from M. charantia, B. balsamifera, and, positive control, remdesivir.

4.1.1.1. Docking studies of the remdesivir with SARS-CoV-2 receptor-binding domain (RBD)

The docking simulation of remdesivir **(9),** set on targeting the catalytic site of SARS-CoV-2 RBD remdesivir exhibited a binding affinity of -6.0 kcal/mol (Table 4.1.1). Moreover, remdesivir was able to exhibit hydrogen bonding to Gly 496 and Gln 498, bifurcated H-bonding to Gln 493 and Tyr 453, as well as hydrophobic interactions involving a pi-pi bonding to Tyr 449 and Tyr 505, and alkyl-alkyl binding with Arg 403 (Figure 4.1.2.). The

compound was able to form interactions with several residues in the RBD active sites, particularly Arg 403, Gln 493, Tyr 453, Gly 496 and Gln 498.

4.1.1.2. Docking studies of *Momordica charantia* phytochemicals with SARS-CoV-2 receptor-binding domain (RBD)

Tormentic acid was docked, set on targeting the catalytic site of SARS-CoV-2 RBD, wherein it exhibited a binding affinity of -6.7 kcal/mol with a single hydrogen bond to LYS 378. Ganoderic acid Y, ligand with the second-highest binding affinity, exhibited a docking score of -6.5kcal/mol, interacting with LYS 378, TYR 380, and TYR 508. These are followed by pomolic acid interacting to ASP 405 through hydrogen bonding, as well as, showing a docking score of -6.4kcal/mol. On the other hand, both ganoderic acid U and phytolaccoside B showed the least binding affinities out of *M. charantia* phytochemicals with a docking score of -6.1kcal/mol; wherein phytolaccoside B participated in H-bonding interactions to LYS 458, SER 459, and ARG 466; at the same time, ganoderic acid U was bound to ARG 403, TYR 453 and GLY 496 through H-bonding.

4.1.1.3. Docking studies of *Blumea balsamifera* phytochemicals with SARS-CoV-2 receptor-binding domain (RBD)

Arnicolide D acid was docked, set on targeting the catalytic site of SARS-CoV-2 RBD, wherein it exhibited a binding affinity of -6.3 kcal/mol and participated hydrogen bonds to SER 375, THR 376, ARG 408. Nigakilactone K, ligand with the second-highest binding affinity among *B. balsamifera* phytochemicals, showed a docking score of -5.7 kcal/mol and interacted with THR 376 through H-bonding. Retinol, ligand with the least binding affinity to RBD, exhibited a binding affinity of -5.4 kcal/mol and participated in H-bonding with SER 371, LYS 378, and PRO 384. Among phytochemicals from *B. balsamifera* docked with SARS-CoV-2 RBD, only arnicolide D was able to interact with an amino acid residue involved in SARS-CoV-2 RBD/hACE2 complex—i.e., ARG 408.

4.1.1.4. Drug-likeness, ADME, and Toxicity

Six out of eight docked phytochemicals were subjected for drug-likeness, ADME, and toxicity analysis—i.e., ganoderic acid U **(1),** ganoderic acid Y **(2),** phytolaccoside B **(3)**, pomolic acid **(4),** tormentic acid-methyl ester **(5),** and arnicolide D **(6)**, including remdesivir **(9)** for reference (Table 4.1.2)—since, retinol **(6)**, and nigakilactone K **(7)** did not pass the minimum docking score threshold of -6.0kcal/mol.

4.1.1.5. Drug-likeness predicted by Lipinski's rule of 5

Among six phytochemicals tested for drug-likeness, ganoderic acid U**,** ganoderic acid Y**,** pomolic acid**,** and arnicolide D passed Lipinski's rule of five, hence, druggable; but tormentic acid-methyl ester, the top-scoring ligand in the docking analysis, as well as phytolaccoside B, and remdesivir**,** the reference drug, violated two or more rules set by Lipinski. Moreover, the estimated solubility (ESOL) reveals that only arnicolide D was water soluble, whereas all phytochemicals and remdesivir were poorly soluble. In addition to this, only ganoderic acid U, phytolaccoside B and tormentic acid-methyl ester exhibited high gastrointestinal absorption; the reference drug remdesivir also has low human intestinal absorption value. On the other hand, MlogP, defined by the partition coefficient between *n*-octanol and water ($\log P_{o/w}$) which describes the lipophilicity of a compound (Daina et al., 2017), determined that all phytochemicals except ganoderic acid Y exhibited lipophilicity following Lipinski's rule of five.

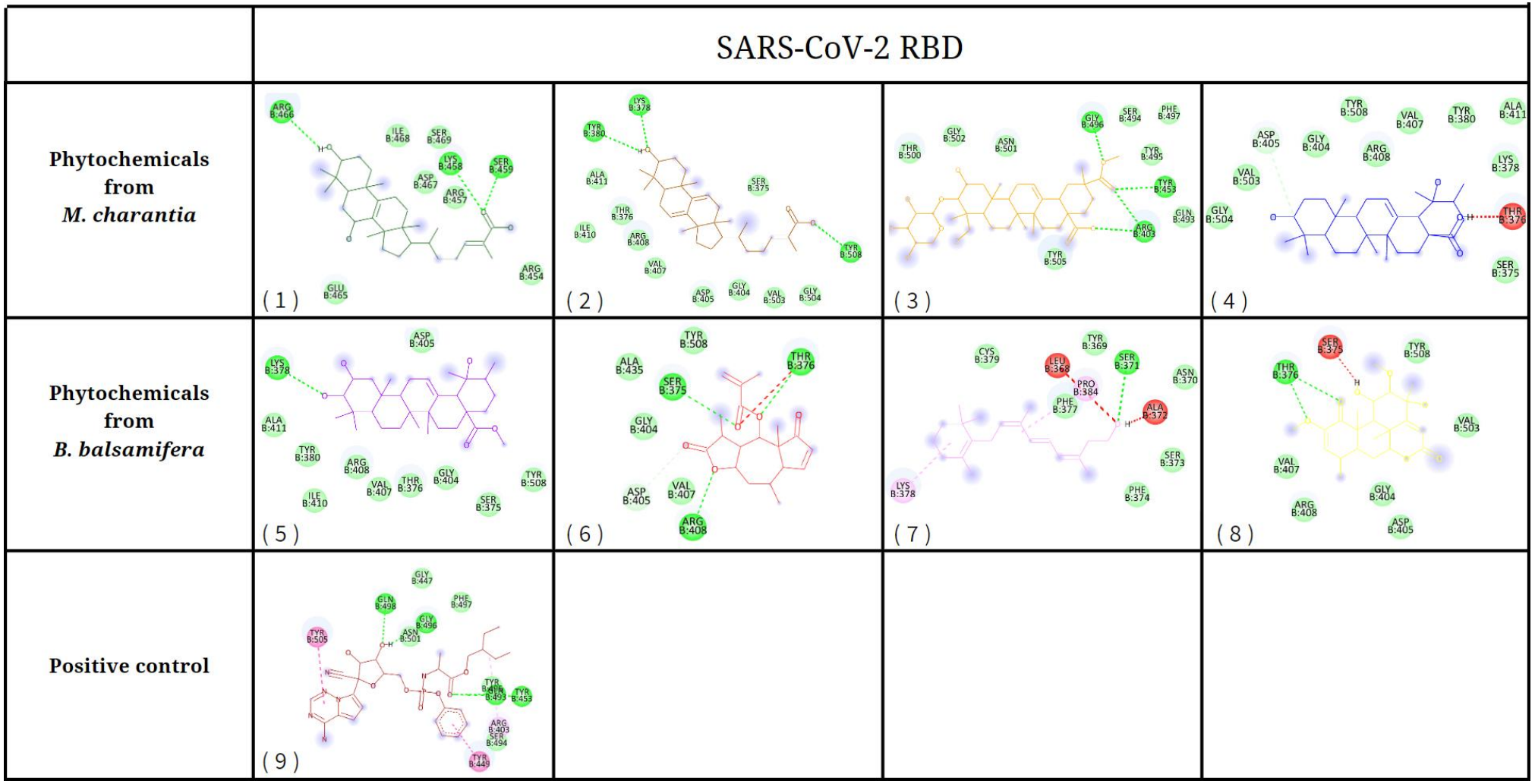


Figure 4.1.2. Visualized output of ligand with the lowest energy and least root mean square deviation (RMSD) was chosen for visualization. 2D interactionsof SARS- COV-2 receptor-binding proteinith (1) ganoderic acid U, (2) ganoderic acid Y, (3) phytolaccoside B, (4) pomolic acid, (5) tormentic acid-methyl ester, (F) arnicolide D, (7) retinol, (8) nigakilactone K and (9) remdesivir

Group	Cpd.	H-Bond Donor	H-Bond Acceptor	GI Absorption	ESOL	MLogP	Drug-likeness
Phytochemicals from *M. charantia*	1	3	4	High	-6.42	4.87	Yes
	2	2	3	Low	-6.94	7.32	Yes
	3	6	11	Low	-5.09	1.66	No
	4	3	4	High	-6.44	4.97	Yes
	5	3	5	High	-6.15	4.33	No
Phytochemicals from *B. balsamifera*	6	0	5	Low	-3.01	2.39	Yes
Positive control	9	4	12	Low	-4.12	0.18	No

Figure 4.1.3. Drug-likeness of phytochemicals from M. charantia, B. balsamifera, and, positive control, remdesivir based on Lipinski's rule of 5.

4.1.1.6. Toxicology predicted by ADMETLab 2.0

As SARS-CoV-2 mainly affects the respiratory tract, along with a carcinogenicity prediction, respiratory toxicity was also added as a parameter. All phytochemicals docked were confirmed to be non-toxic to the respiratory system, apart from phytolaccoside B posing high risks as a respiratory toxicant. On the other hand, arnicolide D is the only compound determined to be non-carcinogenic, all other phytochemicals, including remdesivir, were carcinogenic.

Group	Cpd.	Respiratory Toxicity	Carcinogenicity
Phytochemicals from *M. charantia*	1	No	High risk
	2	No	High risk
	3	High risk	High risk
	4	No	High risk
	5	No	High risk
Phytochemicals from *B. balsamifera*	6	No	Non-carcinogenic
Positive control	9	No	High risk

Figure 4.1.4. Toxicity risks of phytochemicals from M. charantia, B. balsamifera, and, positive control, remdesivir predicted by ADMETLab 2.0.

4.2 In silico analysis of Pandanusphenol A and alpha-glucosidase enzymes

4.2.1 Molecular docking analysis

The active sites of the proteins were determined from their respective papers (Ren et al., 2011; Sim et al., 2008, 2010; Tagami et al., 2013). N-terminal maltase glucoamylase (PDB ID: 2qmj) is an exception to this, as the residues involved in the active site are not indicated in the paper (Sim et al., 2008). Instead, the active site was determined for this particular case by locating the co-crystallized acarbose ligand in the PDB file itself.

Nine docking poses were generated by AutoDock Vina and the pose with the highest binding affinity (lowest binding energy measured by kcal/mol) for each ligand-receptor complex as presented on the table below. The binding energy of a complex is the summation of all the interactions involved (H-bonds, electrostatic torsions, van der Waals, unfavorable connections, etc). The lower the binding energy of an interaction is, the higher is its affinity and presumed the more stable and favorable.

Compound	Binding energy kcal/mol			
	CTMGAM	NtMGAM	NtSI	a-glucosidase
acarbose	- 6.8	-5.8	-4.4	-7.2
pandanusphenol A	-7.8	-6.9	-6.9	-7.3

Figure 4.2.1: Binding energy of the receptor-ligand complexes

Table 4.2.2 is a summary of receptor-ligand interactions that are taken into account in the calculation of their binding energy. Also included are information on the number of hydrogen bonds formed and total interacting residues. Hydrogen bonds are one of the strongest intermolecular attractions, though weaker than ionic or covalent bonds. Their presence can be a great indicator of the stability of the receptor-ligand complex, but the impact of other intermolecular interactions must also be considered, as they could produce a significant binding affinity as shown in the next page. See Figure 4.2.3 which presents the receptor-ligand interactions in 2D.

Refer to Figure 4.2.3: CTMGAM/pandanusphenol A. With C-terminal maltase, the highest-scoring docking pose of pandanusphenol A is stabilized by pi-alkyl/alkyl interactions with ILE1587, PHE1427, and MET1421. The aromatic rings of TRP1369, PHE1427, TRP1355 form pi-interactions with the alkyl groups and aromatic rings of pandanusphenol A. The overall score of this complex is -7.8 kcal/mol.

Refer to Figure 4.2.3: NTMGAM/pandanusphenol A. With N-terminal maltase, the highest-scoring docking pose of pandanusphenol A is stabilized in part by pi-interactions with the aromatic rings of TRP406, which forms a pi-pi T-shaped interaction with the same phenolic ring of the ligand where ASP542 forms a pi-anion interaction. MET444 also forms a pi-sulfur interaction with this same ring. The second phenolic ring of the ligand is stabilized by a pi-sigma with ALA576, which also hydrogen bonds with the hydroxyl hydrogen donor attached to the phenolic ring. The overall score of the complex is -6.9 kcal/mol.

Refer to Figure 4.2.3: NTSI/pandanusphenol A. With N-terminal sucroisomaltase, the highest-scoring docking pose of pandanusphenol A is stabilized by three hydrogen bonds from ARG555, ASP472, and LYS509, with the lone hydroxy group of the ligand and the oxygen atoms on its two methoxy groups, respectively. ASP571 forms a pi-anion bond with the first ring, further stabilized by the pi-pi T-shaped interaction by TRP435. The second ring is stabilized by alkyl and pi-sigma bonds with LEU233. The overall score of the complex is -6.9 kcal/mol.

Refer to Figure 4.2.3: a-glucosidase/pandanusphenol A. With alpha-glucosidase, the highest-scoring docking pose of pandanusphenol A is stabilized by two conventional

hydrogen bonds by ASP469 and ALA234 with the hydrogen of the hydroxyl group and the oxygen atom of one of the methoxy groups, respectively. Alkyl bonds were formed by PHE476, MET70, and ALA234. The aromatic rings of PHE601 and TRP329 form pi-pi t-shaped interactions with one of the phenolic rings. The second ring is stabilized further by a pi-anion bond from ASP232 and a pi-alkyl from ALA234. The overall score of the complex is -7.3 kcal/mol.

Interaction	CTMGAM (PDB: 3top)		NTMGAM (PDB: 2qmj)		NtSI (PDB: 3lpp)		a-glucosidase (PDB: 3w37)	
	acarbose	pandanus-phenol A	acarbose	pandanus-phenol A	acarbose	pandanus-phenol A	acarbose	pandanus-phenol A
Conventional hydrogen bond	GLU1451 GLN1158 ARG1455 ASP1526 TYR1167 ARG1510		TYR605 PHE450 THR205 ASP542 LYS480	ASN543	ASP231 LYS509 ASP632 TYR529	ASP472 ARG555 LYS509	ASN237 LYS506 ASP568 ASP357	ALA234 ASP469
Pi-stacking		TRP1355						
Pi-sigma				ASN543		LEU233		
Pi-alkyl/Alkyl		PHE1427 MET1421 ILE1587		PHE450 TYR299 PHE575		TRP327		MET470 PHE476
Pi-Pi T-shaped		TRP1369		TRP406		TRP435		TRP329 PHE601
Pi-Anion				ASP542		ASP571		ASP232
Pi-sulfur				MET444				
Unfavourable donor-donor		GLN1372						
Unfavourable acceptor-acceptor					TYR529			
No. of residues contributing to van der Waals forces	15	11	12	7	10	5	12	8

Figure 4.2.2: Summary of receptor-ligand interactions of acarbose and pandanusphenol A with alpha-glucosidase enzymes C-terminal maltase glucoamylase, N-terminal maltase glucoamylase, N-terminal sucroisomaltase, and beetroot alpha-glucosidase

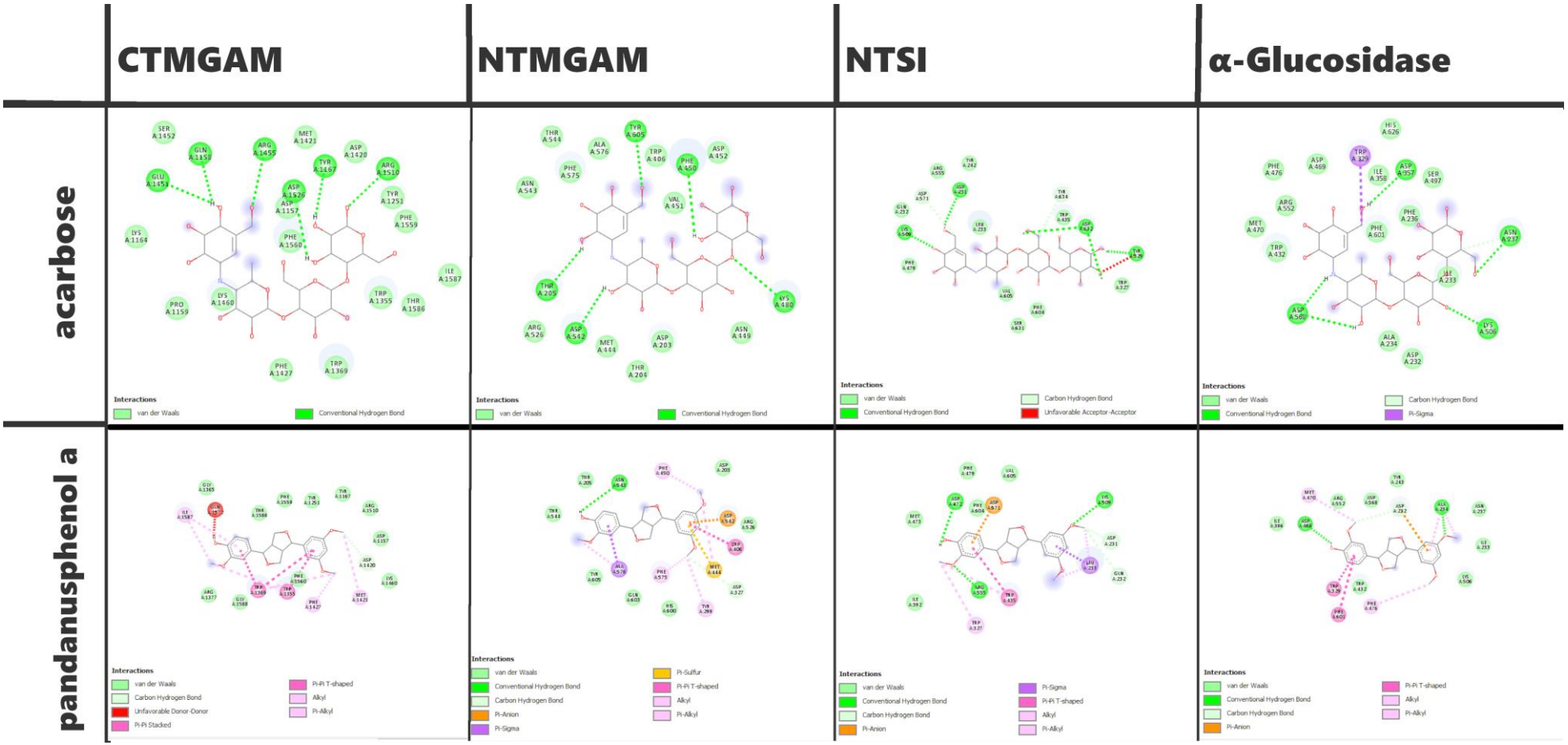


Figure 4.2.3: A schematic of the receptor-ligand interactions of acarbose (standard drug) and pandanusphenol A (experimental molecule) with alpha glucosidase enzymes C-terminal maltase-glucoamylase, N-terminal maltase glucoamylase, N-terminal sucroisomaltase, and beetroot alpha glucosidase in 2D.

4.2.2 In silico prediction of pandanusphenol A pharmacokinetics, druglikeness, and toxicity

The chemical formula of pandanusphenol A is $C_{21}H_{24}O_6$, with a molecular weight of 371.41 g/mol. It has 5 rotatable bonds, 6 hydrogen bond acceptors, and 1 hydrogen bond donor. Its TPSA, a function of polarity, is 66.38, and its LOGP, a function of lipophilicity, is 2.76, a consensus value from iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT computations. This positive LogP value indicates that the molecule is lipophilic and can easily pass through the lipid bilayer of cells. The acceptable ranges are LOGP > 5.88 and TPSA > 131.6. The TPSA and LOGP values are used in the BOILED-Egg model to predict intestinal absorption and brain permeability. It is predicted to be soluble by the generated LogS values from the ESOL and Ali models, and moderately soluble by the SILICOS-IT model.

In line with its lipophilic nature, pandanusphenol A is predicted to have a high gastrointestinal absorption rate. This is in contrast to acarbose, which has a low gastrointestinal absorption rate. This attribute helps acarbose to stay in the brush borders of the intestinal lumen where the alpha-glucosidase enzymes are located, converting complex carbohydrates into simple absorbable sugars. In a diabetic patient, acarbose is helpful in the inhibition of these enzymes to delay the absorption of sugar in the blood, thus preventing hyperglycemia. Therefore, pandanusphenol A is not comparable to acarbose in terms of location or mechanism of action according to in silico data, and may not stay long enough in the intestinal lumen to bind to the alpha-glucosidase enzymes.

Also, pandanusphenol A is predicted to be a blood-brain barrier permeant, which might indicate neuromedical properties. To further this, in silico results indicate that it might be a CYP2D6 inhibitor. CYP2D6, also known as the cytochrome P450 enzyme, is a well-studied enzyme located in the liver, but can also be found in other organs, including the brain (Peñas-LLedó & LLerena, 2014)**.** Peñas-LLedó & LLerena (2014) further note that this enzyme is involved in the metabolism of a significant number of neurological, psychiatric, and addictive drugs that act on the central nervous system, like antidepressants, antipsychotics, and opioids. It also eliminates and metabolizes 25% of clinically approved drugs, as well as activates a number of prodrugs (Wang et al., 2009). It is highly polymorphic between individuals. CYP2D6 inhibitors can lead to decreased CYP2D6 activity and thus decreased metabolic and elimination rate of a CYP2D6-metabolized drug (that is, CYP2D6 substrates). Individuals with overexpressed CYP2D6 metabolise CYP2D6-substrate drugs more quickly, which results in decreased efficacy—CYP2D6 inhibitors counteract this (Teh & Bertilsson, 2012).

Pandanusphenol A passed Lipinski's, Ghost's, Veber's, Egan's, and Muegge's drug-likeness criteria based on molecular weight, lipophilicity, and hydrogen bond donors and acceptors with zero violations. However, it failed the drug lead-likeness test with one violation, as its molecular weight is greater than the threshold, 350 g/mol.

Using ORISIS Property Explorer, pandanusphenol A was predicted to be non-toxic, with no indication for mutagenicity, tumorigenicity, irritating effects, and reproductive effects.

4.3. In silico analysis of Mappain as a chemotherapeutic agent to proteins associated with cancer.

4.3.1 Molecular docking analysis

Binding Energy kcal/mol						
Compound	**P53 hotspot mutation**	**Estrogen receptor-alpha [Erα]-positive**	**Progesterone receptor**	**Mortalin**	**CDK4**	**MEK1**
Mappain	-7.6	-6.0	-7.6	-7.7	-7.2	-9.0
Imatinib (+ control)	-8.9	-8.1	-8.5	-9.2	-8.9	-10.4
Palbociclib (+ control)	-8.2	-6.7	-9.0	-8.8	-8.8	-10.0

Figure 4.3.1 Binding energy values of Mappain against cancer growth-related genes alongside commercially used drugs for chemotherapy.

The binding affinity (in kcal/mol) of Mappain and other ligands (positive controls: Imatinib & Palbociclib) to selected proteins associated with cancer development as shown in Figure 4.3.1. Mappain successfully binds with the selected cancer-related proteins, it has the highest binding affinity with MEK1 at -9.0 kcal/mol, and the lowest with Estrogen receptor at -6.0 kcal/mol. In addition to that, it has shown a relatively lower binding energy to selected proteins when compared with compounds used as drugs for chemotherapy.

In reference to Figure 4.3.2. The molecular docking of Mappain with (PDB ID: 3D06) was stabilized by Pi-interactions such as Pi-Cations and Pi-Anions. Some of the aromatic rings which contain Pi-alkyl/alkyl interactions also contributed to the stabilization of the ligand-receptor interaction, as well as the formation of hydrogen bonds. The molecular docking of Mappain with (PDB ID: 5GS4) was stabilized by Pi-alkyl/Alkyl interactions. Van Der Waals interactions are also observed contributing to additional stabilization. The molecular docking of Mappain with (PDB ID: 1SQN) was stabilized by Pi-Sigma interactions in the first aromatic ring with ILE699. Pi-Alkyl/Alkyl further contributed to the stabilization by attaching themselves to the ligand's chain. The molecular docking of Mappain with (PDB ID: 4KBO) was stabilized by hydrogen bonds from the aromatic rings. The molecular docking of Mappain with (PDB ID: 3G33) was stabilized by Pi-Cation interactions from the first aromatic ring. The second ring has Pi-Alkyl/Alkyl interaction, as well as hydrogen bonds – other Pi-Alkyl/Alkyl interactions, are attached to the ligand's chain, and other hydrogen bonds were also formed. The molecular docking of Mappain with (PDB ID: 7PQV) was stabilized by Pi-Alkyl/Alkyl interactions in the first aromatic ring – as well as hydrogen bond formation. The second aromatic ring has Pi-Anion interactions. A Pi-sigma interaction as well as other Pi-Alkyl/Alkyl interactions further contributed to the stabilization of the ligand-protein. In addition to this, all of the Mappain-protein interactions were all stabilized by van der Waals forces.

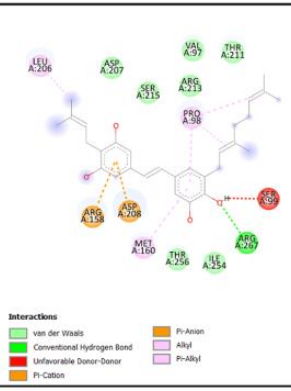
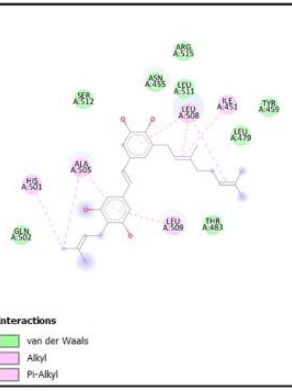
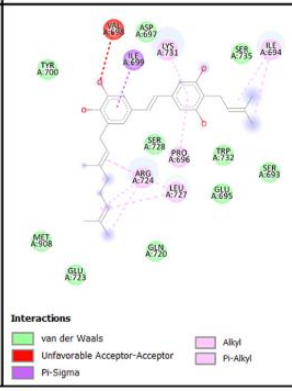
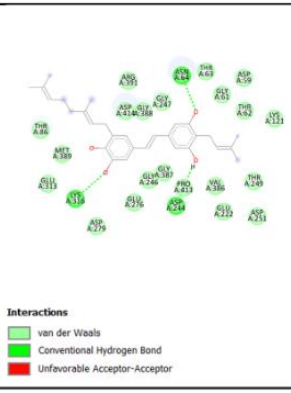
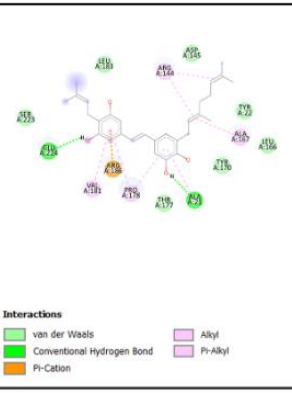
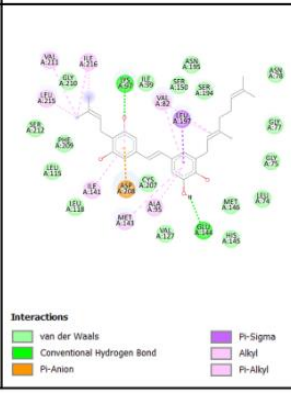
	P53 hotspot mutation (PDB ID: 3D06)	Estrogen receptor-alpha [Erα]-positive (PDB ID: 5GS4)	Progesterone receptor (PDB ID: 1SQN)	Mortalin (PDB ID: 4KBO)	CDK4 (PDB ID: 3G33)	MEK1 (PDB ID: 7PQV)
Mappain						

Figure 4.3.2: A schematic of the receptor-ligand interactions of Mappain (experimental molecule) with proteins associated with cancer in 2D.

4.3.2 Drug-likeness

Lipinski's Rule of Five						
Compound	**Molecular Weight (g/mol) <500**	**Lipophilicity (MLogP) <5**	**H-bond Donors <5**	**H-bond Acceptors <10**	**Rule Violations <2**	**Drug-Likeness**
Mappain	448.59 g/mol	4.77	4	4	0	YES
Imatinib (+ control)	493.60 g/mol	2.15	4	6	0	YES
Palbociclib (+ control)	447.53 g/mol	2.03	2	6	0	YES

Figure 4.3.3 Lipinski's Rule of Five for absorption, distribution, metabolism, and excretion (ADME) analysis of isolated compound of Mappain alongside commercially used drugs for chemotherapy.

The pharmacokinetic properties of Mappain and other ligands (positive controls: Imatinib & Palbociclib) is shown in Table 2. The Druggability of the compounds was assessed based on Lipinski's Rule of Five: molecular weight (less than 500 Daltons), lipophilicity (MlogP less than 5), h-bond donors (under 5), and acceptors (under 10). Mappain shows a high-level level of drug likeness, with zero Lipinski violations.

4.3.3 Toxicity Prediction

Toxicity					
Compound	**Mutagenicity**	**Tumorigenicity**	**Irritant Effect**	**Reproductive Toxicity**	**Solubility (logS)**
Mappain	None	None	None	High Risk	- 5.42
Imatinib (+ control)	None	None	None	None	- 4.38
Palbociclib (+ control)	None	None	None	High Risk	- 4.53

Figure 4.3.4 Predicted toxicity parameters and solubility of the Mappain and commercially used drugs for chemotherapy.

The toxicity parameters and the solubility of Mappain and other ligands (positive controls: Imatinib & Palbociclib) is shown in Table 3. Based on the results retrieved from ORISIS Property Explorer, Mappain exhibits a high risk of reproductive toxicity. Nevertheless, it does not exhibit any toxicity in other areas such as mutagenicity, tumorigenicity, and irritant effect.

5. Discussion

5.1. *Blumea balsamifera* and *Momordica charantia* phytochemicals *in silico analysis*

Remdesivir is an anti-viral drug directly targeting single-RNA viruses such as SARS-CoV, and MERS-CoV (Beigel et al., 2020). Moreover, Remdesivir was able to bind to RNA-dependent RNA polymerase (RdRp), a SARS-CoV-2 molecular target, and limits its conformational changes crucial in viral replication and transcription (Gordon et al., 2020).

Although it was able to form interactions with several residues in the RBD active sites, particularly Arg 403, Gln 493, Tyr 453, Gly 496 and Gln 498, current docking analysis revealed that remdesivir had weaker binding affinity with SARS-CoV-2 RBD compared to other molecular targets of the disease.

As for phytochemicals from *M. charantia*, ganoderic acid U interacted with the specified amino acid residues that define the SARS-CoV-2 RBD/hACE2 interactions—i.e., H-bonding with ARG 403, TYR 453, and GLY 496, respectively. This implies that the H-bonding formed by ganoderic acid U to RBD can interfere with the formation of the necessary RBD/hACE2 complex. Additionally, Aminu et al. (2021) reported that phytolaccoside B exhibits a docking score of -7.1kcal/mol against the spike protein of SARS-CoV-2, interacting with Ala713, Tyr1047, Gln564, and Phe565 which are not amino acid residues specific to the RBD which is located within the S1 subunit of the protein—i.e., amino acid sequence THR 333 to PRO 527 composes RBD (Q. Wang et al., 2020).

On the other hand, among phytochemicals from *B. balsamifera* docked with SARS-CoV-2 RBD, only arnicolide D was able to interact with an amino acid residue involved in SARS-CoV-2 RBD/hACE2 complex—i.e., ARG 408; hence, suggesting possible role to interfere with the complex. In addition to this, nigakilactone K and retinol not only exhibited lower binding affinities compared to the reference drug, remdesivir, but also were below the minimum threshold for compound suitable as drug candidates which is -6.0 kcal/mol recommended by Hiremath et al. (2021). While there is no existent molecular docking analysis for retinol as a potential inhibitor of any SARS-CoV-2 molecular targets, other retinoids such as adapalene, fenretinide, etretinate and isotretinoin exhibited high binding affinities to SARS-CoV-2 protein (Shoemark et al., 2020). As for arnicolide D, and nigakilactone K, this is the first report on their inhibitory role against a SARS-CoV-2 molecular target, specifically the RBD.

Furthermore, Lipinski rule of five was used as basis to analyze the drug-likeness, and pharmacological activities of the phytochemicals from *M. charantia* and *B. balsamifera* for possible development as orally active drugs (Lipinski, 2004). Ganoderic acid U, ganoderic acid Y, pomolic acid and arnicolide D were determined to have drug-like properties; wherein only arnicolide D which is predicted to be soluble and shows good lipophilic characteristic. Solubility is indicative if a compound can be easily excreted out of the body, at the same time, good solubility properties make for efficient formulation during drug development and good drug absorption (Alavijeh et al., 2005). Such phytochemicals which exhibited desirable water solubility and lipophilicity properties likely exhibits oral bioavailability; in that, it is largely influenced by such solubility and lipophilicity (Mandlik et al., 2016)—i.e., drug candidate potentially can escape elimination through the gastrointestinal tract and enter the systemic circulation to reach its therapeutic site (Price & Patel, 2021). However, remdesivir, the reference drug, was not orally bioavailable, it is delivered through other routes and is an exemption to Lipinski's rule (Lipinski, 2004)--i.e., it is delivered intravenously (Beigel et al., 2020; Cao et al., 2020). For this reason, phytochemicals which does not exhibit oral bioavailability based on Lipinski's rule of five can be further explored through other delivery routes.

5.2. IN SILICO ANALYSIS OF PANDANUSPHENOL A AND ALPHA-GLUCOSIDASE ENZYMES

The molecular docking results show that pandanusphenol A has lower binding energy and thus higher binding affinity with all the target receptor proteins than the standard drug, acarbose. Acarbose is most effectively bound to beetroot alpha-glucosidase, then C-terminal maltase, N-terminal maltase, and least to N-terminal sucro-isomaltase. For pandanusphenol

A, it had the highest binding affinity to C-terminal maltase, then beetroot alpha-glucosidase, with both N-terminal maltase and sucro-isomaltase tying for least.

Both ligands bind more favorably to C-terminal maltase and alpha-glucosidase than either N-terminal maltase and sucro-isomaltase. Notably, this result corroborates with the report of Sim et al., (2010), stating that acarbose inhibits the C-terminal subunit more efficiently than its N-terminal due to its additional 21 residues in its active site, allowing it to cleave longer substrates like acarbose.

A primary difference between them is that the interactions of acarbose are dominated by hydrogen bonds, while the interactions of pandanusphenol A are dominated by pi-bonds. This is because acarbose has 14 hydrogen bond donors, compared to pandanusphenol A which has only one. On the other hand, the aromatic rings of pandanusphenol A facilitate the formation of pi-bonds.

Inversely, pandanusphenol A has hydrogen bond acceptors, those being the oxygen atoms on the furofuran lignan ring at the center of the molecule. However, this in silico study shows that they do not participate in interactions at all.

While a hydrogen bond on its own is a strong intermolecular force, which can contribute 2-40 kcal/mol to the overall binding energy of a structure depending on a variety of factors (Steiner, 2002), these in silico results are showing that pandanusphenol A has a higher binding affinity than acarbose on the glucosidases with its pi-interactions. The phenolic rings of pandanusphenol A are held together by the furofuran lignan ring at the center, which, although the in silico studies have not shown it to participate in intermolecular interactions, seems to allow the two phenolic rings to flex in conformations that enable them to participate in non-covalent bonding. Consistent in all the highest-scoring binding pose, the phenolic rings of pandanusphenol A enable it to have pi-interactions with the residues. Less consistently, the lone hydroxyl group enables it to donate a hydrogen proton and the oxygen of the three methoxy groups to accept a hydrogen to form hydrogen bonds.

5.3. In silico analysis of Mappain as a chemotherapeutic agent to proteins associated with cancer.

The results of the molecular docking simulation of Mappain are comparatively lower in binding affinity to all targeted proteins compared to standard drugs such as Imatinib and Palbociclib. Mappain had the highest binding affinity with the protein MEK1 followed by Mortalin, progesterone receptor & p53 core domain, CDK4, and the lowest binding affinity was with Estrogen-Receptor Alpha.

As for the pharmacokinetic properties of Mappain, it was noted that it has a favorable drug-likeness as it passed Lipinski's rule of five for the following: it has a Molecular Weight of 448.59 g/mol (less than 500 Daltons), MlogP of 4.77 (less than 5), 4 H-bond donors (less than 5), 4 H-bond acceptors (less than 10), and with no Lipinski Rule Violations. The toxicity test showed a high risk of reproductive toxicity and none for the other toxicity parameters.

Engineering the Mappain compound by adding adjuvants may produce better quality for its binding affinity - which could produce more interactions for better stability. This could also help in reducing or removing the toxicity effects it contains for the reproductive. Stilbene compounds may possess the ability to act as adjuvants (Y. Lee et al., n.d.). With that being said, Mappain may also help treating cancers by acting as co-adjuvant in chemotherapy.

6. Conclusion

Molecular docking has progressed dramatically leading to the advancement into variety of scientific fields including, but not limited to, molecular biology, biophysics, and

pharmacology. The growing need for molecular docking has resulted in a variety of ways that can improve and provide new tools. Furthermore, the scientific investigations, as well as other studies, show that in silico techniques, when combined with other breakthroughs (e.g., crystallography, spectroscopy, HTS, and toxicological studies) and classical experiments, are an essential asset in medicinal chemistry. Indeed, molecular docking reached an excellent tier of development, as epitomized by the vastness of in silico molecular docking publications. This study has tested the promise of conducting this type of research in university setting which will help students apply their knowledge of biological principles. The comprehensive method outlined in this study wishes to help students in applying this type of research as a potential thesis study under health research.

The study has offered top-ranking phytochemicals including tormentic acid-methyl ester, ganoderic acid Y from M. charantia, and arnicolide D from B. balsamifera against SARS-CoV-2 spike RBD. Among these, arnicolide D was determined to be biologically safe, and pharmacokinetically effective to be delivered orally. It is recommended for arnicolide D to be tested against other molecular targets for SARS-CoV-2 to identify potential multiple-targeting capabilities, and further screening through in-vitro and in-vivo assays. On the other hand, it is predicted that pandanusphenol A has a higher affinity than acarbose to the given alpha-glucosidase enzymes; pharmacokinetic studies predict the molecule to be a brain-barrier permeant and a CYP2D6 inhibitor, insinuating that it might have neuromedical properties; it is also predicted to be nontoxic. Having passed the drug-likeness criteria on SwissADME with no violations, *Pandanusphenol A* seems to be a promising drug candidate. Lastly, Mappain may act as an inhibitor to selected proteins related to cancer as it successfully binds with the selected cancer targets, while taking note of its lower binding affinity compared to standard drugs. It also showed high-risk reproductive toxicity, although it passed the other toxicity parameters. This exploration can function as a complement to wet lab approaches which can aid in decision making, envisioning innovative thoughts, and offering solutions to problems that cannot be tested due to design difficulties and high expenditure.

This conclusion should, however, be taken skeptically, as molecular docking techniques may not produce accurate results. Sethi et al. (2020) discussed several success stories on using molecular docking approaches in searching for a lead molecule for drug discovery, noting the cruciality of computational tools to computer-aided drug design and as a resource-saving technique. But this approach also comes with limitations, the biggest being due to its lack of confidence to give accurate binding energies, as intermolecular forces are not accurately predicted. Other factors include the role of water molecules, the effects of the solvent, the effects of entropy, and the actual flexibility of the protein, which are challenges that limit the accuracy of molecular docking simulations. Enzyme experiments are still therefore needed to confirm the results and to determine if the mechanism of action is inhibitory or agonistic, as molecular docking simulations alone cannot predict it. Furthermore, molecular dynamics studies may also be helpful in elucidating the stability of the binding of the molecule of interest.

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Predictive Ability of Visit-to-visit Glucose Variability on Chronic Kidney Disease Among Diabetes Patients

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Abstract

Problem statement: Diabetes prevalence is increasing over the years, with 537 million adults living with diabetes in 2021. Chronic kidney disease (CKD) is the 12th leading cause of death and mainly due to diabetes, and its treatment cost increases as disease progresses. However, disease monitoring using hemoglobin A1c (HbA1c) in low- and middle-income countries are not optimal. Recent studies explored the use of visit-to-visit glucose variability (GV) as an additional monitoring parameter.

Objectives: To compare the predictive ability of different visit-to-visit GV measures, in terms of HbA1c and fasting plasma glucose (FPG) on CKD among type 2 diabetes (T2D) patients.

Brief methods: A retrospective cohort of T2D patients were obtained from Ramathibodi Hospital. 25 features were included in the analysis. Visit-to-visit GV were measured using HbA1c coefficient of variation (CV), HbA1c standard deviation (SD), FPG-CV and FPG-SD. Survival analyses were performed using Cox proportional hazard regression (COX) and random survival forest (RSF) to handle censored data. Permutation importance was performed with RSF to rank the features. Complete case analyses were performed.

Results: Total of 40662 T2D patients were included in the study, with 4594 patients with CKD throughout their follow-up. HbA1c-CV, HbA1c-SD, FPG-CV, and FPG-SD were significant in COX and ranked among top 10 variables in permutation importance of RSF. FPG-CV and FPG-SD ranked higher than HbA1c-CV and HbA1c-SD.

Significance of findings: Visit-to-visit HbA1c and FPG variability could be used as additional monitoring parameters, especially when HbA1c testing or continuous glucose monitoring is unavailable.

Keywords : Type 2 diabetes, Glucose variability, Chronic Kidney Disease, Cox proportional hazard regression, Random survival forest

1. Introduction

Diabetes is a chronic, non-communicable disease, which manifest when the body could not produce enough insulin or utilize the insulin produced effectively, causing increased blood sugar level (Federation, 2021). Type 2 diabetes (T2D) is the most common type of diabetes, which consists of over 90% of the diabetes cases (Federation, 2021). Prevalence of diabetes increases over the years, with an estimated number of 537 million adults (10.5%) living with diabetes worldwide in year 2021(Federation, 2021). Western Pacific Region accounts for 38% of the total number of diabetes cases in the world and Thailand ranks top 4 in terms of number of people with diabetes in this region, with a prevalence rate of 11.6%(Federation, 2021).

CKD is the 12th leading cause of death in the world and the main cause of CKD is diabetes(Bikbov et al., 2020). As cost of treating patients with CKD increases with disease progression to end stage renal failure with the need of renal replacement therapy, it is important to effectively prevent or prolong disease progression. Timely control of blood glucose and good control have been shown to prevent disease progression of CKD among diabetes patients (Hahr & Molitch, 2015; Jung, 2021). However, this is a challenge for low- and middle-income countries as a study shown that only 23% of diabetes patients who have their disease under control (Manne-Goehler et al., 2019).

In recent years, studies have been carried out to investigate glucose variability as another predictor for CKD among diabetes patients. Glucose variability can be measured via continuous glucose monitoring (short-term) or using visit-to-visit hemoglobin A1c (HbA1c) or fasting plasma glucose (FPG) (long-term). HbA1c coefficient of variation (HbA1c-CV) has been shown to be associated with reduced kidney function among diabetic patients who achieved HbA1c target (C.-L. Lee, Chen, Wu, & Tsai, 2020). HbA1c standard deviation (HbA1c-SD) as a variability measure has been shown to relate to progression to end stage renal failure among diabetic patients with CKD stage 3-4 (M.-Y. Lee, Huang, Chen, Chiou, & Wu, 2018). These studies used traditional statistical approaches – Cox proportional hazard regression (COX)(M.-Y. Lee et al., 2018) and mixed effect model for repeated measures(C.-L. Lee et al., 2020). Machine learning models have been used to predict the development of CKD among T2D patients. However, glucose variability measures are not included in the models and none of them include models that handle right-censored data (Allen et al., 2022; Dong et al., 2022; Thammasudjarit, 2021).

2. Objectives

The study objective is to compare the predictive ability of different glucose variability measures, in terms of HbA1c-CV, HbA1c-SD, FPG-CV and FPG-SD on CKD among T2D patients, using traditional statistical model (COX) and machine learning model (Random survival forest).

3. Materials and methods

This study used a retrospective cohort design with routine clinical data (year 2011-2019) obtained from CEB Data Warehouse, Faculty of Medicine Ramathibodi Hospital. Adult (≥ 18 years old) T2D patients with two or more measurements of HbA1c or FPG in the first two years were included in the study. Those who are on dialysis or diagnosed with CKD on the first visit will be excluded. CV and SD will be calculated using all the measurements in the first 2 years of follow up. Hba1c-CV, HbA1c-SD, FPG-CV and FPG-SD were included as predictor of interest in their respective models, which means four different models were developed for each of the glucose variability measure. CKD was determined using International Classification of Diseases 10th revision codes and based on laboratory findings (i.e. estimated glomerular filtration rate of less than 60 for three consecutive times in six months).

Complete case analysis was performed. 25 features had been included for analyses, which include demographic, laboratory monitoring, comorbidities, and drug use. For COX, stepwise selection through back-and-forth procedure was performed for feature selection, all data were used for building the model and bootstrapping was performed to obtain bootstrapped concordance index. On the other hand, random survival forest was trained with 70% and tested on 30% of the dataset. Hyperparameter tuning was performed using RandomizedSearchCV with 5-fold cross-validation to obtain the set of hyperparameters with

the best test score, which were used to build the final models. COX was analyzed using R software and random survival forest was analyzed using Python software. This study has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (COA. MURA 2022/100)

4. Results

Our study population consisted of 40662 T2D patients, with mean age of 57.2 years and mostly female (61.7%). More than half of the population has hypertension (67.9%) and dyslipidemia (67.3%) at baseline. Mean body mass index (BMI) is 28.1 kg/m^2, which is at obese category based on WHO guideline for Asian population (Consultation, 2004). Table 1 shows the baseline characteristics of the study population.

All glucose variability measures (HbA1c-CV, HbA1c-SD, FPG-CV and FPG-SD) were shown to be significant in their respective final COX model (Table 2) with the HR ranging from 1.00 to 5.13 and C-index at 0.743 to 0.752 in predicting CKD among T2D patients. In random survival forest (Table 3), we found that all glucose variability measures ranked at number 3, with the C-index at 0.732 to 0.744 in test data set. FBG-SD random survival forest model has the smallest gap between train and test data set and hence least risk of overfitting whereas FBG-CV model has the largest gap.

From COX models, we observed similar trends for other risk factors, where male gender, national health insurance scheme, increase in age, BMI, SBP, and use of insulin and sulphonylurea, comorbid of hypertension, and prior diagnosis of CVD and DR, were associated with increased risk of developing CKD. Whereas the use of metformin and increase in haemoglobin level were associated with reduced risk in developing CKD. Statin use shows a negative association with CKD, but only limited to HbA1c glucose variability measure models.

Table 1 Baseline Characteristics of Study Population

	N = 40662		
	n	**%**	**% missing**
Age (years), mean (SD)	57.2	13.9	0
Male	15560	38.3	0
Insurance type			
Government	16220	50.3	0
National health insurance	3774	11.7	0
Social security insurance	1229	3.8	0
Others	11043	34.2	0
BMI (kg/m^2), mean (SD)	28.1	5.7	45
SBP (mmHg), mean (SD)	141.9	20.2	42
DBP (mmHg), mean (SD)	83.1	9.6	42
Total Cholesterol (mg/dL), mean (SD)	198.4	63.2	23
LDL Cholesterol (mg/dL), mean (SD)	129.3	42.0	33
HDL Cholesterol (mg/dL), mean (SD)	47.0	13.0	38
Triglyceride (mg/dL), mean (SD)	171.6	158.1	31
Hemoglobin (g/dL), mean (SD)	13.2	1.7	42
HbA1c-CV	0.07	0.08	41
HbA1c-SD	0.67	0.87	41
FPG-CV	0.12	0.14	26
FPG-SD	25.98	40.67	26

	N = 40662		
	n	**%**	**% missing**
Comorbidities/Complications			
Hypertension	27617	67.9	0
Dyslipidemia	27363	67.3	0
Cardiovascular disease	546	1.3	0
Diabetes retinopathy	346	0.9	0
Chronic kidney disease	4594	11.3	0
Drug use			
Number of antihypertensive medications, mean (SD)	0.87	1.12	0
Statins	18648	45.9	0
Alpha-glucosidase inhibitors	2540	6.2	0
Biguanides	23615	58.1	0
DPP-4 inhibitors	2838	7	0
GLP-1 receptor agonists	138	0.2	0
Insulin	3305	8.1	0
Meglitinide	53	0.1	0
SGLT2 inhibitors	250	0.6	0
Sulphonylureas	7752	19.1	0
TZD	2290	5.6	0

BMI: body mass index; CV: coefficient of variation; DBP: diastolic blood pressure; DPP-4: Dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NHSI: ; SBP: systolic blood pressure; SD: standard deviation; SGLT2: sodium glucose transporter protein 2; TZD: thiazolidinedione

Table 2 Cox Proportional Hazard Regression

	N=7928			N=7928	
	HR	**95% (CI)**		**HR**	**95% (CI)**
HbA1c-CV	**5.13**	**2.61-10.07***	**HbA1c-SD**	**1.16**	**1.08-1.23***
Age	1.02	1.02-1.03*	Age	1.02	1.02-1.03*
Male	2.18	1.92-2.48*	Male	2.19	1.93-2.49*
BMI	1.03	1.02-1.04*	BMI	1.03	1.02-1.04*
Insurance: National health insurance	1.38	1.18-1.63*	Insurance: National health insurance	1.37	1.17-1.62*
Insurance: Others	0.92	0.79-1.06	Insurance: Others	0.92	0.79-1.06
Insurance: Social security insurance	1.13	0.81-1.58	Insurance: Social security insurance	1.14	0.81-1.59
SBP	1.01	1.00-1.01*	SBP	1.01	1.00-1.01*
Hypertension	1.80	1.45-2.23*	Hypertension	1.80	1.46-2.23*
Metformin	0.74	0.65-0.84*	Metformin	0.75	0.65-0.85*
Insulin	1.36	1.16-1.61*	Insulin	1.37	1.16-1.61*
Sulphonylurea	1.19	1.03-1.37*	Sulphonylurea	1.19	1.03-1.37*
Statins	0.85	0.75-0.96*	Statins	0.85	0.75-0.96*
Cardiovascular disease	4.16	3.38-5.11*	Cardiovascular disease	4.19	3.41-5.14*
Diabetes	4.01	3.11-5.16*	Diabetes	4.06	3.15-5.22*

	N=7928			N=7928	
	HR	**95% (CI)**		**HR**	**95% (CI)**
retinopathy			retinopathy		
Hemoglobin	0.75	0.73-0.78*	Hemoglobin	0.75	0.72-0.78*
Concordance index (SE)	**0.744 (0.008)**		**Concordance index (SE)**	**0.743 (0.008)**	
	N=9269			**N=9269**	
	HR	**95% (CI)**		**HR**	**95% (CI)**
FBG-CV	**3.50**	**2.57-4.77***	**FBG-SD**	**1.00**	**1.00-1.00***
Age	1.02	1.02-1.03*	Age	1.02	1.01-1.03*
Male	2.26	2.01-2.55*	Male	2.28	2.02-2.57*
BMI	1.03	1.01-1.04*	BMI	1.02	1.01-1.04*
Insurance: National health insurance	1.40	1.21-1.63*	Insurance: National health insurance	1.40	1.20-1.62*
Insurance: Others	0.89	0.78-1.03	Insurance: Others	0.89	0.77-1.02
Insurance: Social security insurance	1.18	0.87-1.60	Insurance: Social security insurance	1.19	0.88-1.62
SBP	1.01	1.00-1.01*	SBP	1.01	1.00-1.01*
Hypertension	1.79	1.47-2.18*	Hypertension	1.80	1.47-2.19*
Metformin	0.73	0.64-0.82*	Metformin	0.73	0.65-0.83*
Insulin	1.18	1.00-1.38*	Insulin	1.23	1.05-1.45*
Sulphonylurea	1.20	1.05-1.37*	Sulphonylurea	1.22	1.06-1.40*
Statins	0.90	0.80-1.01	Statins	0.90	0.80-1.02
Cardiovascular disease	4.02	3.31-4.88*	Cardiovascular disease	4.16	3.43-5.06*
Diabetes retinopathy	3.99	3.11-5.13*	Diabetes retinopathy	4.14	3.22-5.32*
Hemoglobin	0.75	0.72-0.78*	Hemoglobin	0.75	0.72-0.78*
Concordance index (SE)	**0.752 (0.007)**		**Concordance index (SE)**	**0.748 (0.007)**	

BMI: body mass index; CI: confidence interval; HR: hazard ratio; SBP: systolic blood pressure; SE: standard error

Table 3 Random Survival Forest

Hyperparameters for tuning	**n_estimators**	50, 100, 200, 300, 400, 500			
	min_samples_split	5, 10, 15, 20			
	max_leaf_nodes	10, 20, 30, 40, 50			
	max_depth	2, 4, 8, 16			
		HbA1c-CV	**HbA1c-SD**	**FPG-CV**	**FPG-SD**
Chosen hyperparameters	**n_estimators**	500	200	100	400
	min_samples_split	20	15	10	5
	max_leaf_nodes	50	30	50	30
	max_depth	4	8	8	4
Concordance index (Test dataset)		0.732	0.735	0.749	0.744
Concordance index (Train dataset)		0.787	0.827	0.850	0.787
Permutation ranking importance for the glucose variability measure of interest		#3	#3	#3	#3

5. Discussion

This study provides an insight on the use of visit-to-visit glucose variability measure as a new approach for diabetes monitoring. All glucose variability measures that we studied (HbA1c-CV, HbA1c-SD, FPG-CV, FPG-SD) has fair concordance index of about 0.73-0.74, in predicting CKD among T2D patients. This could be an useful finding for low- and middle-income countries as FPG is a cheaper test than HbA1c (Gillett et al., 2015). In addition, FPG is a more commonly used test in Thailand, with 95.1% patients receiving a FPG test in their last visit in year 2018. Only 76.4% of diabetes patients receiving at least one HbA1c test during the last 12 months in year 2018 (Sakboonyarat et al., 2021).

Currently, there are evidence that DPP-4 inhibitors and GLP-1 receptor agonists has variability-reducing effect (Kovatchev, 2019). Hence, more measures aiming to reduce glucose variability instead of just merely reducing HbA1c should be further studied.

6. Conclusion

Visit-to-visit HbA1c and FPG can be an additional monitoring parameter in diabetes management. Further studies could compare the use of HbA1c reading with HbA1c-CV and HbA1c-SD and similarly for FPG.

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9. Appendices

None.

10. Author(s) Biodata (50 words)

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Study of raft forming anti-reflux preparation of mucilage from *Basella alba* L.

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Abstract

Ceylon spinach (*Basella alba*) is a plant in the Basellaceae family. The arial part of the plant contains a large amount of mucilage, consisting of polyuronides that may have raft-forming property. The objectives of this research were to study the physico-chemical properties of mucilage isolated from Ceylon spinach, to formulate suspension of the mucilage and to evaluate the raft-forming effect of the suspension via in vitro. The results showed that the isolated mucilage had a swelling index of 10.07 ± 0.03, pH 6.61 ± 0.11, and loss on drying of 8.95% ± 0.51. The chemical composition of the mucilage was determined by thermal hydrolysis and analyzed by thin layer chromatography. TLC chromatogram revealed bands corresponded to glucose and galactose. Suspensions were prepared using the isolated mucilage at the concentrations of 6%. Different types and concentrations of suspending agents, hydroxypropyl methylcellulose (HPMC) at 0.75% and 1.00% and carboxymethylcellulose sodium (Na CMC) at 0.50% and 0.75% were used. It was found that the formulation with the best physico-chemical properties was the one containing Na CMC at 0.50%. The percentage of sedimentation volume of the suspension was 44%. It was easily redispersed by 10 times of human shaking. However, raft-forming performed under simulated gastric acid conditions revealed that no raft was formed in all formulations.

Keywords : Basella alba, mucilage, raft forming, heartburn, swelling index

1. Introduction

Heartburn and acid reflux are primary symptoms of gastro-oesophageal reflux disease (GERD). Reflux of gastric acid into oesophagus most often occurs after meals. A variety of non-prescription products are used for the symptomatic treatment of heartburn, acid indigestion, and acid reflux disorders such as antacids, bismuth-containing products, and alginate rafting products. Alginate rafting products provide rapid onset and longer duration of action by a physical rather than a chemical or pharmacological mechanisms. Alginates isolated from brown seaweed are natural polysaccharide polymers composed of L-guluronic and D-mannuronic acid. Alginates and alginic acids rapidly form viscous gel with low density in the acid environment of stomach. Molecular weight and the ratio of L-guluronic and D-mannuronic acid residues of alginate affect the strength of the gel. In addition, calcium shows ability to cross-link alginic acid polymers to form raft and increase the raft strength. The alginate raft was proved to provide sufficient viscosity to reduce gastric acid reflux disorders (Mandel, 2000, p.669–690, Yaswantrao, 2015, p.178-192).

Basella alba L. is a perennial succulent vine which belongs to family Basellaceae. It is commonly known as Ceylon spinach, Malabar spinach, vine spinach, or Puk Pang Kao (Thai). The fresh leaf, thick heart-shaped with mucilaginous texture is used as vegetable. Several phytochemical compounds such as proteins, alkaloids, polysaccharides, phenols, flavonoids, and carotenoids were found in the plant (Kumar, 2013, p.53-58, Deshmukh, 2014, p.153-165). Mucilage isolated from *B. alba* is composed of D-galactose as a major component. It is viscous with low swelling capacity and exhibits suitable pH for skin (5.3 - 5.4). The mucilage was reported to use as gelling agent in cosmetics and provided a good stability (Palanuvej, 2009, p.837-850, Haneefa, 2012, p.1642-1648). Additionally, mucilage

can be used for pharmaceutical aid as thickener, water-retention agent, suspending agent, and film former (Jani, 2007, p.90-98, Tosif, 2021, p.1-24). The present study was to isolate mucilage from stems and leaves of *B. alba* and the isolated mucilage was subjected to formulate the raft forming anti-reflux preparations. As well as physical properties of the preparations were studied.

2. Objectives

The objectives of the study are to formulate raft forming anti-reflux preparations using isolated mucilage from stems and leaves of *B.* alba and to evaluate physical properties of the preparations.

3. Materials and methods

3.1 Chemicals

Glucose, galactose, fructose, and arabinose were purchased from Sigma-Aldrich. Excipients used for preparation of suspension were hydroxypropyl methylcellulose (HPMC; from Dow company, USA), sodium carboxymethyl cellulose (Na CMC; from Shandong Yulong chemical technology, China), sodium bicarbonate (from Tokuyama corporation, Japan), calcium carbonate (from Konoshima chemical, Japan), and saccharin sodium (from S. Tong chemicals, Thailand). All other chemicals and reagents used were of analytical grade. Deionized water was used throughout the experiments.

3.2 Plant material

The fresh stems and leaves of *Basella alba* L. planted in Huachiew Chalermprakiet University, Bang Phli district, Samut Prakan province, Thailand were used in this study.

3.3 Extraction and isolation of mucilage from *Basella alba* L.

The fresh stems and leaves were rinsed with tap water and dried at 45°c using hot air oven before grounded into coarse powder by blender. The plant powder (1.543 kg) was defatted by soaking in petroleum ether (4 L) overnight. The defatted material was sent to extract by boiling in deionized water (18 L) for 30 minutes. After the extract was cool to room temperature, it was filtered through eight-fold of muslin cloth. Ethanol was poured into the filtrate in the ratio of (1:1) and gently mixed. For complete precipitation, the mixture was kept in an airtight container at 2°c for 2 days. Then precipitate was separated and washed with cold ethanol for three times before dried at 40°c. The dry precipitate was ground and passed through a 100-mesh sieve.

3.4 Evaluation of physicochemical properties of the isolated mucilage

Physical appearance of the isolated mucilage was evaluated by observing its color, odor, and consistency.

3.4.1 pH measurement

The isolated mucilage (0.25 g) was dispersed in 25 mL deionized water and sent to measure pH value using pH meter at room temperature.

3.4.2 Swelling index determination

The initial volume of the isolated mucilage (1 g, accurately weighed) was measured using a 25 mL graduated cylinder. Ethanol (1 mL) was added to moisten the extract and 25 mL deionized water was added. The mixture was shaken vigorously every 10 minutes for 1 hour then allowed to stand for 24 hours at room temperature. After 24 hours, the sediment volume was measured, and the swelling index was calculated by taking the ratio of swollen volume to the initial volume of 1 g.

3.4.3 Weight loss on drying

One gram of the isolated mucilage, accurately weighed, was used to determine weight loss on drying. Sample was oven-dried at 105°c for 2 hours until constant weight was obtained (± 0.0005 g). The percentage loss on drying was calculated by the equation as shown below.

$$\% \text{ Loss on drying} = 100\ (W_1\text{-}W_2)/W_1$$

Where: W_1 = initial weight of sample, g

W_2 = final weight after drying, g

3.4.4 Thin layer chromatography analysis

The isolated mucilage (30 mg) was hydrolyzed with 3 mL of 10% hydrochloric acid at 100°c for 2 hours and concentrated before analyzing by thin layer chromatography. Glucose, galactose, fructose, and arabinose (10 mg/mL) were used as reference standards.

Chromatography was performed on 10 x 10 cm aluminum plates precoated with 0.2 mm layers of silica gel 60 F_{254} (E. Merck, Germany). Sample and standard solutions, each 1 µL, were applied on the plates as 2 mm wide bands, positioned 10 mm from lower edge of the plate. The mobile phase was acetonitrile-water 8.5:1.5 (v/v). Pre-saturated chamber (30 minutes at room temperature) was used for development of the plates with a distance of 95 mm from lower edge of the plate using ascending mode. The developed plates were detected with color reaction using 10% aqueous sulfuric acid, the color reaction occurred when heat at 105°c for 15 minutes.

3.4.5 Fehling's test for monosaccharides

Fehling's reagent was freshly prepared by combining solution A (7 g of copper sulfate in 100 mL water) and B (35 g of potassium tartrate and 12 g of sodium hydroxide in 100 ml water) in the ratio of 1:1. One mL of Fehling's reagent was added to 2 mL of hydrolyzed mucilage and mixed. The mixture was heated in water bath for 5 minutes. The brick red precipitate would confirm the presence of monosaccharides.

3.4.6 Fourier transform infrared spectral analysis

Functional groups presenting in the isolated mucilage were determined by fourier transform infrared (FTIR) spectrometer (PerkinElmer Spectrum 100). The spectrum was recorded between 4000 and 650 cm^{-1}.

3.5 Preparation of raft forming anti-reflux suspension using the isolated mucilage

Five different formulations (F1 – F5) were prepared using the isolated mucilage at the concentration of 6% w/v as shown in table 1. HPMC and Na CMC were used as suspending agents in different concentrations. Calcium carbonate was used as antacid. Sodium bicarbonate was used as carbon dioxide generating agent. Methyl- and propyl-paraben were used as preservatives. Saccharin sodium and peppermint oil were used as sweetening and favoring agents, respectively. Primarily the isolated mucilage and suspending agents each was separately dispersed in DI water before mixing. Calcium carbonate, sodium bicarbonate, and saccharin sodium were dissolved in DI water and added. Then, the remain excipients were added and stirred continuously till uniform dispersion was obtained.

Table 1 Composition of raft forming anti-reflux suspensions (F1 - F5)

Excipients	Amount (%W/V)				
	F1	F2	F3	F4	F5
Isolated mucilage	6.00	6.00	6.00	6.00	6.00
HPMC	-	0.75	1.00	-	-
Na CMC	-	-	-	0.50	0.75
Calcium carbonate	1.60	1.60	1.60	1.60	1.60
Sodium bicarbonate	2.67	2.67	2.67	2.67	2.67
Saccharin sodium	1.00	1.00	1.00	1.00	1.00
Peppermint oil	0.20	0.20	0.20	0.20	020
Methylparaben	0.40	0.40	0.40	0.40	0.40
Propylparaben	0.06	0.06	0.06	0.06	0.06
DI water q.s.	100.00	100.00	100.00	100.00	100.00

3.6 Evaluation of physical properties of suspension

3.6.1 Physical appearance

Physical appearance of suspension was evaluated by observing its color, odor, and consistency.

3.6.2 pH measurement

Suspension was sent to measure pH value using pH meter at room temperature.

3.6.3 Sedimentation volume

Each formulation (25 mL) was transferred to a 25 mL graduated cylinder and allowed to stand at room temperature without agitation. The volume occupied by the solute was recorded at 1, 4, 8, and 12 weeks. The percentage sedimentation volume was calculated by the equation as shown below.

$$\% \text{ Sedimentation volume} = 100\ (V_u)/V_o$$

Where: V_u = ultimate sediment volume, mL

V_o = original sediment volume, mL

3.6.4 Redispersibility rate

Each formulation (25 mL) was transferred to a 25 mL graduated cylinder and allowed to stand at room temperature. On 1, 5, 10, 15, 20, 30, and 45 days the cylinders were moved upside down until the sediment was uniform redispersed and the number of times used to invert the cylinders was recorded.

3.6.5 Raft forming

Each formulation (2 mL) was added in 0.1 M hydrochloric acid (10 mL) and maintained at 37°c in 30 mL glass beaker for 10 minutes. The character of raft formation was observed and recorded.

4. Results and discussion

The plant powder (1.543 kg) was defatted with a non-polar solvent, petroleum ether to remove all non-polar compounds before extracted by boiling in deionized water. The aqueous extract was viscous liquid after left to cool at room temperature. And mucilage was isolated from the aqueous extract by ethanol precipitation at low temperature (2°c). The isolated mucilage (76.88 g) was obtained as brown to grey green fragment shown in figure 1 with the percentage yield of 4.98% w/w of plant powder. The percentage loss on drying of the mucilage was 8.95% ± 0.51. The pH and swelling index of the mucilage dispersion were 6.61 ± 0.11 and 10.07 ± 0.03, respectively. The acid-hydrolysis mucilage was tested with Fehling's reagent and the brick red precipitates occurred that confirmed the presence of monosaccharides. Additionally, thin layer chromatography analysis of the acid-hydrolysis mucilage exhibited spots comparable to glucose and galactose which in agreement with

previous reports. Chatchawal (2010) indicated that D-galactose was the major monosaccharide in the mucilage extracted from stems and leaves of *B. alba* by TLC analysis (p.101-112). Gas chromatography analysis of mucilage extracted from aerial parts of *B. alba* revealed the composition of galactose, glucose, arabinose, rhamnose, and galacturonic acid in the ratio of 41:16:24:5:13 (Palanuvej, 2009, p.837-850).

The FTIR spectrum of the isolated mucilage indicated the presence of stretching vibration of hydroxyl groups (O-H) at 3,369 cm^{-1} (broad), stretching vibration of alkyl group (C-H) at 2,928 cm^{-1}, stretching vibration of carboxyl and carbonyl (COO^-) at 1,638 cm^{-1}, bending vibration of alkyl group (C-H) at 1,369 cm^{-1}, and polysaccharide group (C-O-C) at 1,015 cm^{-1}. The band corresponding to carboxylate group indicated the presence of uronic acid which is commonly found in mucilage (Quintero-García, 2021, p.1-18). As well as the wavenumbers between 800-1200 cm^{-1} characterizes the fingerprint region for carbohydrate (Singh, 2014, p.713-725).

Figure 1 The isolated mucilage from *Basella alba* L.

Five different formulations (F1 – F5) were prepared using the isolated mucilage at the concentration of 6% w/v. Among five formulations of raft forming anti-reflux suspensions, F1 did not contain any suspending agents, and consequently the isolated mucilage could not suspend throughout the liquid media. Accordingly, F1 was not subjected to further studies. Physical appearance and pH of F2 - F5 are shown in table 2. The viscosity of all suspensions increased when the amount of suspending agents increased. Formulations prepared with HPMC (F2 and F3) were found to be more viscous than that with Na CMC (F4 and F5). The highest viscosity was shown in F3 whereas the lowest viscosity was shown in F4.

Table 2 Physical appearance and pH of suspensions (F2 - F5)

Physical appearance	F2	F3	F4	F5
Color	Brown	Brown	Brown	Brown
Odor	Peppermint	Peppermint	Peppermint	Peppermint
Taste	Sweet	Sweet	Sweet	Sweet
Viscosity	+++	++++	+	++
pH*	9.12 ± 0.01	9.11 ± 0.01	9.13 ± 0.01	9.12 ± 0.01

(+) = very low; (++) = low; (+++) = moderate; (++++) = high

* Values are presented as mean ± SD; n = 3

The percentage sedimentation volume of suspensions (F2 - F5) over storage period of 2 months are shown in table 3. The results showed that sedimentation volumes of suspensions decreased with an increase time of storage and varied depend on concentrations and types of suspending agents. The sedimentation volumes of F2 and F3 which used HPMC as

suspending agent were higher than of F4 and F5 which used Na CMC as suspending agent. At 4 weeks of storage, the sedimentation volumes of F4 and F5 were constant.

Table 3 The percentage sedimentation volume of suspensions (F2 - F5)

Periods	Sedimentation volume (%V/V)			
	F2	F3	F4	F5
1 weeks	60	62	46	42
4 weeks	56	56	44	40
8 weeks	54	54	44	40

Redispersibility rates of each suspension after stand for several days at room temperature were shown in figure 2. The results showed that the redispersibility rates of suspensions increased when the storage periods increased. Furthermore, F4 and F5 which used Na CMC as suspending agent were easily redispersed than F2 and F3 which used HPMC as suspending agent. At 45 days of storage, F4 containing Na CMC at 0.50%. was easily redispersed by 10 times of human shaking.

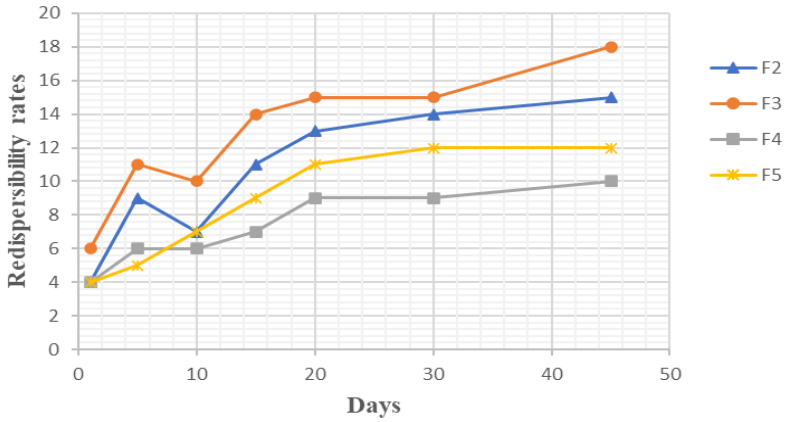

Figure 2 The redispersibility rates of suspension (F2 - F5) after stand for 1, 5, 10, 15, 20, 30, and 45 days at room temperature.

Raft forming systems have been used in the treatment of heartburn and acid reflux which are the symptoms of gastro-oesophageal reflux disease (GERD). Alginates, natural polysaccharide polymers from brown seaweed, have been used to form raft that can act as a physical barrier to reduce the acid reflux. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats on the gastric fluids and acts as a barrier between the stomach and oesophagus to prevent the reflux of the gastric acid into the oesophagus (Yaswantrao, 2015, p.178-192). The character of raft formation of each formulation (F2 - F5) was observed under simulated gastric acid conditions, 0.1 M hydrochloric acid at 37°c for 10 minutes. The results showed that no raft was formed in all formulations. This may be due to the amount of calcium carbonate and sodium bicarbonate in each formulation is not enough to provide raft. Raft formation and raft strength depend on several factors. Calcium ion was reported as an extrinsic factor which increase raft strength by its ability to cross-link polysaccharide polymers. Bicarbonate, another extrinsic factor, acts as a carbon dioxide generating agent which produces carbon dioxide bubbles in the presence of gastric acid. The bubbles are entrapped within the gel matrix allowing the gel to float on the surface of gastric fluid (Mandel, 2000, p.669–690). In addition, the concentration of mucilage as well as its physicochemical properties also impact to raft formation. The process used for drying mucilage after isolation from plant material influences its physicochemical properties. Conventional drying using an oven causes the

collapse of the porous structure of hydrogel which produces a massive volume shrinkage due to the capillary pressure gradient established during the solvent removal. This phenomenon can reduce the consistency and water holding capacity of the mucilage that has a highly aggregated and densely packed without pore (Auriemma, 2020, p.3156).

5. Conclusion

The isolated mucilage from stems and leaves of *B. alba* was composed of glucose and galactose with a swelling index of 10.07 ± 0.03, pH 6.61 ± 0.11, and loss on drying of 8.95% ± 0.51. Suspension containing 6% of the isolated mucilage and 0.5% of Na CMC exhibited good physico-chemical properties. It was easily redispersed by 10 times of human shaking with the percentage of sedimentation volume of 44%. However, raft-forming performed under simulated gastric acid conditions revealed that no raft was formed in all formulations. Different concentrations of mucilage and carbon dioxide generating agent for formulation of good raft forming anti-reflux preparation should be further study.

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Simultaneous Determination of Diosmin and Hesperidin in *Cissus quadrangularis* Capsules by Ultraviolet-Visible Spectroscopy

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Abstract

The aim of this study was to develop and validate the analytical method for simultaneous determination of diosmin and hesperidin in *Cissus quadrangularis* capsules, using UV-visible spectroscopy based on simultaneous equation method. Standard and sample solutions were prepared in 0.2 N NaOH and measured the absorbances at 267.5 and 284.0 nm, as the maximum absorption wavelength of diosmin and hesperidin, respectively. Validation results of showed acceptable linearity of diosmin and hesperidin over the concentration range of 1 – 5 and 4.8 – 24 µg/mL, respectively. Unfortunately, the percentage recoveries and %RSD for hesperidin did not meet the acceptance criteria. The developed method was applied to quantify the content of diosmin and hesperidin in the capsules, the assay result revealed that each 250-mg capsule (125 mg of *C. quadrangularis* powder) contained 29.88 ± 0.08 and 3.176 ± 0.45 mg of diosmin and hesperidin, respectively. However, more specific and precise method, such as high-performance liquid chromatography (HPLC) must be further developed for the estimation of diosmin and hesperidin in multicomponent formulations.

Keywords : Diosmin; hesperidin; Cissus quadrangularis capsules; ultraviolet-visible spectroscopy

1. Introduction

Cissus quadrangularis L. (Vitaceae) or commonly known in Thailand as "Phet Sang Khat" is a medicinal plant that has been used in Ayurveda for very long time. *C. quadrangularis* is a climbing herb with tendrils grown throughout Asia and Africa. Stem and root portions of this plant provide anthelmintic, antibacterial, dyspeptic, digestive, and analgesic effects, including general tonic, especially for the patient with bone fractured. Moreover, many scientific studies reported various potential benefits by using of *C. quadrangularis* stem powders or extracts for the treatment of irregular menstruation, bone fractures, back pain, and hemorrhoids (Brahmkshatriya *et al.*, 2015, pp. 169-173; Stohs & Ray, 2013, pp. 1107-1114). In Thailand, dried powder of *C. quadrangularis* in combined capsules has been widely used as an alternative medicine to relieve hemorrhoid symptoms. The clinical efficacy of 500-mg *C. quadrangularis* powder capsules and micronized purified flavonoid fraction (MPFF) did not show statistically significant difference compared with placebo for the treatment of acute hemorrhoids (Panpimanmas *et al.*, 2010, pp. 1360-1367). Interestingly, several groups of phytochemical constituents are identified from *C. quadrangularis* powders and extracts, such as triterpenoids, carotenoids, phytosterols, tannins, ascorbic acid, calcium oxalate, and flavonoids (Nawghare *et al.*, 2017, pp. 443-445).

The bioflavonoids (i.e., quercetin, diosmin, and hesperidin) are found to be major components in *C. quadrangularis* stem powders. The active constituents that play a crucial role for the treatment and prevention of hemorrhoids are supposed to be diosmin and hesperidin, which are generally found in 9:1 ratio particularly in citrus species. These 2 flavonoid glycosides possess antioxidative, vasoprotective, and venotonic properties by

promoting vascular sustainability and elasticity (Cospite, 1994, pp. 566-573; Ivanova *et al.*, 2018, pp. 61-70). Thus, the amount of diosmin and hesperidin contained in various formulations should be determined or standardized for effective treatment outcomes.

Previous studies have introduced different analytical methods, such as high-performance liquid chromatography (HPLC) (Kanaze *et al.*, 2003, pp. 243-249), and UV-visible spectroscopy (Bennani *et al.*, 2020, pp. 100-107; Ivanova *et al.*, 2018, pp. 61-70; Srilatha *et al.* 2013, pp. 1-4) for concomitant analysis of diosmin and hesperidin in beverages, food supplements, and pharmaceutical dosage forms, but no reports for *C. quadrangularis* powders or extracts. For UV-visible spectroscopy, this technique was found to be a simple, rapid, reliable, economical, and suitable for simultaneous determination of samples in binary mixture. Therefore, the rationale of this study was to determine the quantity of diosmin and hesperidin in *C. quadrangularis* capsules by developed and validated UV-visible spectrophotometry using simultaneous equation method.

2. Objectives

To develop and validate an analytical method for determination of diosmin and hesperidin in *C. quadrangularis* capsules, using UV-visible spectroscopy based on simultaneous equations (Vierodt's method).

3. Materials and methods

3.1 Materials

Diosmin (>85.0% purity) was purchased from Tokyo Chemical Industry (Tokyo, Japan) and Hesperidin (≥80% purity) was purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Sodium hydroxide pellets (NaOH, AR grade) was purchased from Ajax Finechem (New South Wales, Australia) for preparation of 0.2 N NaOH in deionized water. Marketed available 250-mg *C. quadrangularis* capsules (Mho Iang Brand, Kongka Herb, Nakhon Pathom, Thailand), labeled to contain 50 g of *C. quadrangularis* in 100 g of powder, was purchased from a local drugstore in Bangkok, Thailand.

UV spectra and absorbances were recorded using JASCO double-beam UV-visible spectrophotometer model V-630 (Tokyo, Japan) with a pair of matched 1-cm quartz cells. All spectral data were analyzed using Spectra Manager Software.

3.2 Methods

3.2.1 Method development

Preparation of stock standard solutions

Diosmin and hesperidin were weighed accurately about 5 and 12 mg, respectively, into 50-mL volumetric flask, separately. Dissolved and adjusted to the volume with 0.2 N NaOH to obtain diosmin and hesperidin stock standard solution at concentration of 100 and 240 µg/mL, respectively.

Preparation of standard solutions

Diosmin and hesperidin standard solutions were prepared by diluting the stock standard solutions with 0.2 N NaOH to get series of diosmin standard solution at concentrations of 1, 2, 3, 4, and 5 µg/mL. Similarly, a series of hesperidin standard solution at concentrations of 4.8, 9.6, 14.4, 19.2, and 24 µg/mL was also prepared. These solutions were scanned to determine the wavelength of maximum absorbance (λ_{max}) and measured the absorbances at corresponding wavelengths.

Preparation of sample solution

The capsule powder was weighed accurately equivalent to 125 mg of *C. quadrangularis* into a 50-mL volumetric flask. The powder was dissolved in 20 mL of 0.2 N NaOH, shook for 5 min, adjusted to the volume with the same solvent, and mixed. The mixture was filtered through a 0.45-µm filter paper and discarded the first 5 mL of filtrate. Pipetted 2.0 mL of the filtrate into a 50-mL volumetric flask and adjusted to the volume with 0.2 N NaOH to obtain 0.1 mg/mL of *C. quadrangularis* powder.

3.2.2 Method validation

The developed method was validated for specificity, linearity, accuracy and precision according to the ICH and AOAC guideline.

Specificity

Diosmin and hesperidin standard solutions were scanned in the UV range 200 – 400 nm to examine the λ_{max}. Specificity of the method was determined by comparing the pattern of UV spectra obtained from individual and combined standard solution to the spectrum of sample solution.

Linearity and range

Linearity was established by the linear regression analysis of calibration curves. Standard solutions in the concentration range of 1 – 5 µg/mL for diosmin and 4.8 – 24 µg/mL for hesperidin were prepared. The absorbances obtained simultaneously from corresponding wavelengths were plotted against the concentrations to determine the regression equation and correlation coefficient (r). The linearity was accepted when $r > 0.995$.

Accuracy and precision

Accuracy was evaluated by calculating mean recoveries of diosmin and hesperidin using standard addition method (at the 100% level). The samples were prepared in 6 replicates by adding each 5.0 mL of 90 µg/mL diosmin and 10 µg/mL hesperidin standard solution into 25-mL volumetric flasks, containing 5.0 mL of sample solution. Adjusted to the volume with 0.2 N NaOH and mixed. The absorbances of standard addition mixture were measured at the corresponding wavelengths compared with un-spiked sample solution. The accuracy was accepted when percentage recoveries (%recovery) were in range of 97 – 103.

Precision was consequently determined by calculating percentage of relative standard deviation (%RSD) from average %recovery. The precision was accepted when %RSD values were not more than 2.7.

3.2.3 Assay of *C. quadrangularis* capsules

Pooled powder from 20 capsules were accurately weighed accurately and prepared by a stepwise procedure for sample solution (3.2.1), then diluted with 0.2 N NaOH to obtain 0.02 mg/mL of *C. quadrangularis* powder. The absorbances of the resulting solution were measured at the corresponding wavelengths.

3.2.4 Simultaneous equation method

The absorbances of sample mixtures were measured at corresponding λ_{max} of diosmin and hesperidin. The concentration of diosmin (x) and hesperidin (y) in the mixtures were calculated by simultaneous equation using the following formula:

$$C_x = \frac{A_2 ay_1 - A_1 ay_2}{ax_2 ay_1 - ax_1 ay_2} \qquad C_y = \frac{A_1 ax_2 - A_2 ax_1}{ax_2 ay_1 - ax_1 ay_2}$$

Where C_x and C_y are the concentration of diosmin and hesperidin, respectively; A_1 and A_2 are the absorbance of sample solution at λ_{max} of hesperidin (284.0 nm) and diosmin (267.5 nm), respectively; ax_1 and ax_2 are absorptivity of diosmin at 284.0 and 267.5 nm; and ay_1 and ay_2 are absorptivity of hesperidin at 284.0 and 267.5 nm, respectively. The

absorptivity (a) values of diosmin and hesperidin were obtained from the slope of their calibration curves.

4. Results

The developed method was applied to determine the quantity of diosmin and hesperidin in *C. quadrangularis* capsules without the separation of each compound prior to analysis by UV-visible spectroscopy based on simultaneous equation method. In this study, the analytical method was validated in terms of specificity, linearity, accuracy and precision.

4.1 Method validation

Specificity

Absorption spectra of diosmin and hesperidin showed the λ_{max} of 267.5 and 284.0 nm, respectively. Comparisons between combined standard solution and sample solution, the result illustrated that overall spectral pattern were different (Figure 1). Absorption peak of the sample at 267.5 nm was comparable to the standard mixture, suggested that the method might be more specific to diosmin than hesperidin.

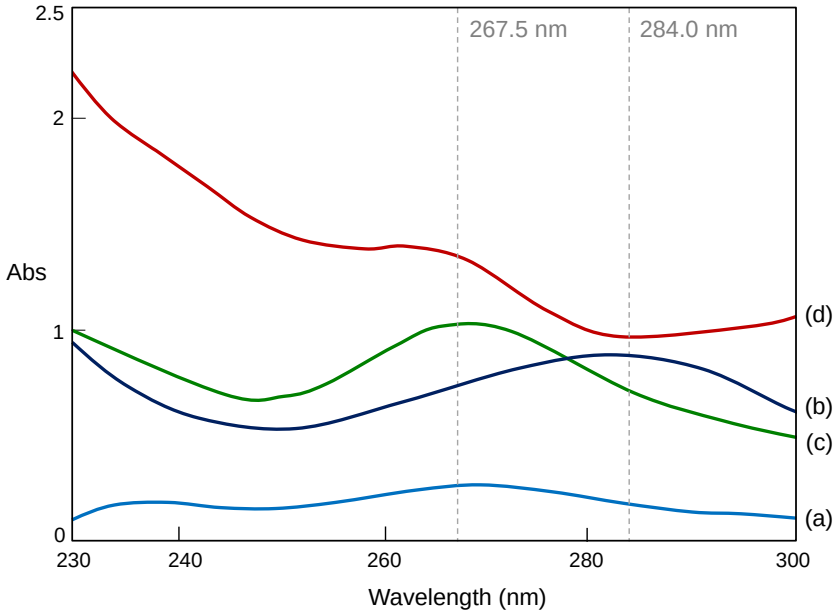

Figure 1 UV overlay spectra of diosmin at 5 µg/mL (a); hesperidin at 24 µg/mL (b); combined standard solution contained 18 and 2 µg/mL of diosmin and hesperidin, respectively (c); and *C. quadrangularis* sample solution (d).

Linearity and range

The calibration curve of diosmin was linear over the concentration range of 1 – 5 µg/mL with the regression equation and correlation coefficient (r) of y = 0.0498x + 0.003 (r = 0.9997), and y = 0.034x + 0.0027 (r = 0.9997) at 267.5 and 284.0 nm, respectively. In similar fashion, hesperidin also showed good linearity over the concentration range of 4.8 – 24 µg/mL with the regression equation and r-value of y = 0.0194x - 0.0063 (r = 0.9999), and y = 0.0304x - 0.0078 (r = 0.9999) at 267.5 and 284.0 nm, respectively.

Accuracy and precision

Using standard addition method for evaluation of analytical method accuracy and precision, 6 replicates of spiked samples were analyzed and calculated the amount of diosmin and hesperidin recovered at the 100% level. The data were displayed in Table 1. For accuracy, %recoveries varied from 97.20 – 97.69% (average 97.47%) for diosmin and 96.88

– 107.8% (average 103.9%) for hesperidin. For precision, %RSD values calculated from mean percentage recoveries were 0.16% for diosmin and 4.73% for hesperidin. These findings suggested that the developed method was accurate and precise for the quantification of diosmin more than hesperidin.

Table 1 Accuracy and precision results for diosmin and hesperidin (n = 6)

No.	Diosmin			Hesperidin		
	Amount added (µg/mL)	Amount found (µg/mL)	%Recovery	Amount added (µg/mL)	Amount found (µg/mL)	%Recovery
1	20.94	20.41	97.45	0.64	0.69	107.8
2	20.94	20.36	97.20	0.64	0.63	98.44
3	20.94	20.46	97.69	0.64	0.69	107.8
4	20.94	20.41	97.44	0.64	0.68	106.3
5	20.94	20.41	97.45	0.64	0.68	106.3
6	20.94	20.43	97.55	0.64	0.62	96.88
	Average		97.47	-	-	103.9
	SD		0.16	-	-	4.92
	%RSD		0.16	-	-	4.73

4.2 Assay of *C. quadrangularis* capsules

Sample solution containing 0.02 mg/mL of *C. quadrangularis* powder was prepared and measured the absorbances in triplicate at 267.5 and 284.0 nm. The amount of diosmin and hesperidin calculated by simultaneous equation (mean ± SD) were found to be 29.88 ± 0.08 and 3.176 ± 0.45 mg/capsule (125 mg of *C. quadrangularis* powder), respectively.

5. Discussion

Determination of diosmin and hesperidin by UV-visible spectroscopy using simultaneous equation method was found to be simple, precise, and accurate. Srilatha, *et al.* (2013) had introduced the success of this analytical method to quantify the amount of diosmin and hesperidin in tablet dosage form (Daflon® 500 mg, each tablet contains diosmin 450 mg and hesperidin 50 mg), using 0.2 N NaOH as a solvent. The results showed satisfied validation parameters in terms of linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), and ruggedness with a simple procedure for sample preparation. Thus, the main concept of previous research was adapted to our study for simultaneous determination of diosmin and hesperidin in *C. quadrangularis* capsules. For method validation, the results of diosmin met the criteria in terms of linearity, accuracy, and precision. On the other hand, the validation results of hesperidin seemed to be unsatisfied especially for specificity and precision. This may due to a very low proportion of hesperidin which usually occurred in combination with diosmin in 1:9 ratio, and the effect of other compounds in the matrix that possibly interfered the measured absorbances. Therefore, an appropriate extraction process must be applied for sample preparation to primarily separate the interferences, resulting to an increase of method specificity. Moreover, most of commercially available *C. quadrangularis* capsules are in combined traditional medicines which the exact quantity of diosmin and hesperidin is unknown. For this reason, the amount of these compounds in *C. quadrangularis* powder was estimated by calculating from total flavonoid content found, which 100 g of *C. quadrangularis* stem powder contained 7.86 g of total flavonoids (Nawghare *et al.*, 2017, pp. 443-445). However, this tentatively estimation was useful to provide a starting information for the preparation of sample solution to contain

appropriate concentrations of diosmin and hesperidin for further analysis, including the setting of accuracy and precision acceptance criteria.

Our findings showed the concept of simultaneous analysis to determine the quantity of diosmin and hesperidin in *C. quadrangularis* capsules without the separation of each compound. Although this analytical method was found to be simple and easy to operate, the presence of other components in the analyte still affected the specificity as mentioned above. Thus, using of more efficient method to quantify and isolate the interested compounds in samples was expected to overcome this problem. Kanaze, *et al.* (2003) had previously reported a reversed-phase high-performance liquid chromatographic method (RP-HPLC) for simultaneous determination of diosmin and hesperidin in Daflon® tablets, including marketed and fresh citrus fruit juices. Compared with the UV-visible spectrophotometric method (Srilatha *et al.* 2013, pp. 1-4), LOQ of hesperidin obtained from HPLC method was noticed to be lower (0.1 vs. 0.42 µg/mL), whereas the other validation parameters were resemble and met the criteria.

6. Conclusion

The analytical method in this study was considered to be simple, accurate and precise, especially for the quantification of diosmin. However, the application of the developed method for simultaneously determination of diosmin and hesperidin in *C. quadrangularis* capsules still had some limitations. Thus, separation technique with qualitative and quantitative analysis, such as high-performance liquid chromatography (HPLC) could be a specific, accurate, and precise method to estimate the content of diosmin and hesperidin in multicomponent formulations for further study.

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Comparison of Traditional Chinese Medicine and Traditional Thai Medicine on Their Theories and Therapeutic Prescriptions in the Treatment of Female Infertility

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ABSTRACT

Objective: To systematize and analyze the differences between traditional Chinese medicine (TCM) and traditional Thai medicine (TTM) on their theories and therapeutic prescriptions for the treatment of female infertility in Thai patients and provide the prescription compatibility of herbal formulas for Thai female infertility. **Methods:** Systematized and analyzed 228 published papers and 161 textbooks on TCM and 87 published papers together with 29 textbooks on TTM and herbal prescriptions for female infertility treatment that were collected from 2008 until July 2018, and the historical texts for TCM documents, and all data from 1782 until July 2018 for TTM from the Medline, Cochrane, CBM, CNKI, and the ThaiJO database. In addition, we referenced books relevant to female infertility in TCM and TTM and analyzed reference lists of relevant articles from the Shanghai University of TCM, Thai National Library, and reviewed numerous TCM prescriptions from Tianfa Hospital, ZhengWenjie TCM Clinic. The methodology used to analyze the prescription patterns included datamining and statistical analysis using IBM SPSS 21.0 for Windows, and IBM SPSS Modeler Subscription (Apriori), which were used to analyze the frequency and association rules among the prescriptions. **Results:** The results showed that TCM and TTM have similar explanations on the principles of getting pregnant, infertility factors, disease mechanism, and therapeutic theories for the treatment of female infertility. The analyzed treatment results show that both TCM and TTM were based on understanding the disease mechanisms and to use a holistic diagnosis pattern, followed by choosing the appropriate treatment options available. The results of TCM and TTM prescription compatibility patterns in the treatment of Thai female infertility showed TCM's most important compatible prescription herbs were "*Bupleurum chinensis* - Dry human placenta, *Cuscuta chinensis* - *Morus alba* - *Curculigo orchioides* - *Epimedium brevicornum*"; TCM prescriptions to treat Thai female infertility focused on the nourishment of Qi and blood, warm and tonify kidney-Yang, regulate Chong and Ren meridians, disperse liver Qi stagnation, promote blood circulation, and remove blood stasis. "*Atractylodes lancea* - *Angelica dahurica*", "*Piper sarmentosum* - *Piper interruptum* - *Zingiber officinale* - *Piper retrofractum* - *Plumbago indica*" were the most compatible herbal found. TTM prescriptions to treat Thai infertility regulate and nourish the four(4) basic body elements, nourish blood, nourish the fire element to eliminate cold inside the body, eliminate blood stasis, and treat all other blood disorders. **Conclusions:** There are similarities between TCM and TTM on the diagnosis and treatment of female infertility; however, there are differences in how TCM and TTM explain the underlying causes of infertility. Both TCM and TTM's diagnoses are based on a holistic view and understanding of the body's organs and systems. Most of the Thai female infertility patients analyzed in this research had a "cold and deficiency pattern", and so the main treatment methods for both TCM and TTM are to prescribe herbs to regulate the menstrual cycle and flow, nourish blood, regulate and treat uterine disease, improve body circulation, and remove blood stasis. There are, however, differences between TCM and TTM in terms

of the specifics herbal prescriptions used to treat infertility, which are based on their specific paradigms and understanding of the root causes of female infertility.

Keywords : female infertility; traditional Chinese medicine (TCM); traditional Thai medicine (TTM); prescription pattern; data mining

Introduction

Female infertility is defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse [1], and is currently becoming a worldwide reproductive health concern. Although not a fatal disease, there are serious impacts on both the physical and mental health of those affected, and it has become a problem for society as a whole [2-3]. According to the Center for Disease Control and Prevention, CDC, the estimated incidence of infertility is gradually increasing [4]. The causes of female infertility are complex, and caused by a range of factors, such as abnormalities of the ovaries, uterus, fallopian tubes, the endocrine system, or there may be other unknown causes. The treatment of female infertility remains a challenge for healthcare providers.

Traditional Chinese medicine (TCM) and Thai traditional medicine (TTM) are two of the most important alternative fields of medicine available in Thailand for the diagnosis and treatment of female infertility. The field of traditional Chinese medicine especially, has developed comprehensive diagnosis and treatment options for female infertility, which have been developed over the past several hundred years.

Traditional Chinese Medicine theory claims that "the kidney controls the reproductive system", and therefore, the kidney's essence plays an important role for the basis of human growth, development, and reproduction [5]. There are several potential causes of female infertility, such as the six external factors and seven emotions (excess of certain emotions), damage of Chong and Ren meridians, and so on, among those, deficiency in the spleen and kidney, stagnation of liver qi, deficiency of blood, qi and yang, and a disorder of Chong and Ren meridians, phlegm and dampness, are believed to be most important causes [6-8]. Therefore, invigorating the kidney and liver, strengthening the spleen, soothing the liver and modifying the patients mental state, promoting blood circulation and removing blood stasis, invigorating the spleen, removing phlegm and dampness, also nourishing qi, yang and blood are the main treatment methods in TCM [9-10]. According to its clinical efficacy and safety [11-12], choosing traditional Chinese medicine to treat female infertility is one of the effective options.

Thai traditional medicine Thai traditional medicine also has comprehensive diagnosis and treatment procedures for gynecological diseases, including female infertility. Thai traditional medicine focuses on the collection and analysis of a patient's comprehensive medical history and comparing it with the factors that lead to gynecological disease according to TTM. "Tard -chao-ruan" is the most basic substance in human life. The imbalance of "Tard -chao-ruan" is a major factor in the progression of any disease. The etiology and pathogenesis of female infertility in Thailand are complex, and are recorded in "Khamphi Mahachotrat". "Prathomjinda", an important TTM textbooks on gynecology, states ~~believes~~ that there are internal and external factors that cause the imbalance of blood and "Tard-chao-ruan" and the imbalance of "the 4 elements" in the patient's body, thus leading to menstrual disorders, as well as other disorders, which are the main causes and pathogenesis of female infertility. Therefore, reconciling and nourishing the blood are the main treatment options for female infertility [13-14].

Traditional Chinese medicine (TCM) and Thai traditional medicine (TTM) have similar but distinct treatments for female infertility; each having an advantage over the other in some respect. The objective of this research is to systematize and analyze the differences between traditional Chinese medicine (TCM) and traditional Thai medicine (TTM) on their theories and therapeutic prescriptions for the treatment of female infertility in Thai patients, and provide the theoretical basis and references for the continued learning exchange between TCM and TTM.

METHODOLOGY

1. DOCUMENT ANALYSIS

Inclusion criteria (published papers and textbooks)

1. Qualitative research on Chinese medicine, Chinese herbal medicine for female infertility treatment is included.
2. No limits to the research methodology.
3. Studies on infertile women with primary and secondary infertility without age limits.
4. All literature published from 1782 until July 2018, published in English, Thai, and Chinese for TTM.
5. Published papers in English, and Chinese on TCM topics from 2008 until July 2018.
6. Relevant textbooks published until 2018.

Exclusion criteria

1. Not a full research report or abstracts of articles/papers (if only abstract was available)
2. Research conducted with samples other than women or infertile couples.
3. Research in a language other than English, Chinese, and/or Thai.

We systematized and analyzed 228 published papers and 161 textbooks on TCM and 87 published papers and 29 textbooks on TTM and herbal prescriptions for the treatment of female infertility collected between 2008 and 2018 (July), historical texts on TCM, and all data from 1782 until 2018 (July) for TTM from the Medline, Cochrane, CBM, CNKI, and the ThaiJO database by using the following search terms: 'infertility', 'female infertility', 'Chinese medicine', 'Chinese herbal medicine', 'Traditional Chinese medicine', 'TCM', 'woman disease', 'Thai Traditional medicine', 'Thai herbal medicine', and 'TTM'. Additionally, we sourced books relevant to female infertility in TCM and TTM and checked reference lists of relevant articles from the Shanghai University of TCM, and the Thai National Library.

2. STATISTICAL ANALYSIS (DATA MINING ANALYSIS)

Data mining and statistical analysis was used to analyze the TCM and TTM prescription patterns for treating female infertility from Tianfa Hospital, ZhengWenjie TCM Clinic from January 2014 – August 2018. Data was input into Excel 2010 and statistical analysis was performed by IBM's SPSS Statistic Base 21.0; specifically, analysis was conducted on herbal use frequency. The statistical software identified the frequency of herb types used in TCM and TTM prescriptions in the treatment of female infertility; herbs with average and above average frequency for us in prescriptions were identified as core herbs.

The Apriori algorithm (an algorithm that is used in mining frequent products sets and relevant association rules.) of the IBM SPSS Modeler Subscription statistical software was used to screen out the association rules of prescriptions: the minimum support in TCM prescriptions is 0.3, the minimum confidence was 0.9, and the minimum support refers to the probability of A and B appearing at the same time, it is a measure of the accuracy of

association rules; confidence refers to the probability that when A occurs, B will probably occur, it is a measure of the importance of association rules; minimum support and confidence determined the lift degree, lift value was more than 1, the larger value of lift referred significance of core herbs in prescription.

Result

1. Frequency analysis of TCM prescriptions for female infertility treatment in Thai Patients.

Result showed two hundred twenty-three (223) TCM prescriptions for female infertility in Thailand were collected. One hundred sixty-two (162) herbs, with a total frequency of 3,182. The top 10 most frequently prescribed traditional Chinese herbs are *Pseudostellaria heterophylla, Eucommia ulmoides, Epimedium brevicornum, Astragalus membranaceus, Lycium barbarum, Cuscuta chinensis, Morus alba, Curculigo orchioides, Atractylodes macrocephala, Glycyrrhiza uralensis.* See table 1.

Table 1 Frequency of TCM herbs prescribed to Thai patients for the treatment of female infertility

Scienctific name	Frequency	frequency rate (%)	Scienctific name	Frequency	frequency rate (%)
Pseudostellaria heterophylla	155	4.9	*Sedum sarmentosum*	84	2.6
Eucommia ulmoides	131	4.1	*Paeonia lactiflora*	83	2.6
Epimedium brevicornum	129	4.1	*Adenophora tetraphylla*	74	2.3
Astragalus membranaceus	128	4	*Codonopsis pilosula*	67	2.1
Lycium babarum	121	3.8	*Salvia miltiorrhiza*	58	1.8
Cuscuta chinensis	108	3.4	*Citrus reticulata*	55	1.7
Morus alba	107	3.4	*Dioscoria opposita*	52	1.6
Curculigo orchioides	107	3.4	*Angelina sinensis*	52	1.6
Atractylodes macrocephala	104	3.3	*Plantago asiatica*	48	1.5
Glycyrrhiza uralensis	104	3.3	*Trichosanthes kirilowii*	45	1.4
Bupleurum chinensis	94	3	*Saposhnikovia divaricata*	41	1.3
Dry human placenta	91	2.9	*Foeniculum vulgare*	40	1.3
Rehmannia glutinosa	89	2.8	*Polygonatum sibiricum*	40	1.3

Source: Analysis based on prescriptions written for treating female infertility between January 2014 and August 2018 at Tianfa Hospital, ZhengWenjie TCM Clinic.

2. Frequency analysis of TCM herb types prescribed to Thai patients to treat female infertility.

The results show that tonic herbs, heat-clearing herbs, and herbs that promote blood circulation and remove blood stasis are used more frequently than other types of herbs. Among those, tonic herbs have the highest frequency used. See table 2.

Table 2 Frequency of TCM herb types prescribed to Thai patients to treat female infertility.

Herbal categories	Frequency	Frequency rate (%)
Tonic herb	39	24.1
Heat-clearing herb	25	15.4
Herb to promote blood circulation and remove blood stasis	19	11.7
Diaphoretic herb	13	8
Diuresis and diffusing dampness herb	9	5.6
Qi-regulating herb	9	5.6
Liver-Pacifying Wind-Extinguishing herb	8	4.9
Phlegm treatment and cough supression herb	7	4.3
Sedative herb	7	4.3

Source: Analysis based on prescriptions written for treating female infertility between January 2014 and August 2018 at Tianfa Hospital, ZhengWenjie TCM Clinic

3. Frequency analysis of TTM prescriptions for female infertility treatment in Thai Patients.

Eighty-five (85) TTM prescription were collected, and 299 herbs were used; the total frequency was 1,341. The top 10 most frequently prescribed TTM herbs were *Piper retrofractum*, *Zingiber officinale*, *Piper nigrum*, *Nigella sativa*, *Plumbago indica*, *Piper interruptum*, *Piper ribesoides*, *Piper sarmentosum*, *Angelica dahurica*, *Cuminum cyminum*, *Myristica fragrans*. See table 3.

Table 3 Frequency of TTM herbs prescribed to Thai patients for the treatment of female infertility

Scienctific name	Frequency	frequency rate(%)	Scienctific name	Frequency	frequency rate (%)
Piper retrofractum	48	3.6	*Lepidium sativum*	16	1.2
Zingiber officinale	48	3.6	*Amomum krervanh*	16	1.2
Piper nigrum	41	3.1	*Allium sativum*	15	1.1
Nigella sativa	35	2.6	*Myristica fragrans*	15	1.1
Plumbago indica	33	2.5	*Tarenna hoaensis*	15	1.1
Piper interruptum	27	2	*Terminalia bellirica*	15	1.1
Piper sarmentosum	26	1.9	*Zingiber cassumunar*	15	1.1
Angelica dahurica	22	1.6	*Anethum graveolens*	14	1
Cuminum cyminum	22	1.6	*Acorus calamus*	14	1
Myristica fragrans	22	1.6	*Phyllanthusemblica*	13	1
Syzygium aromaticum	22	1.6	*Citrus hystrix*	11	0.8
Cyperus rotundus	19	1.4	*Euphorbia antiquorum*	11	0.8
Atractylodes lancea	18	1.3	*Cinnamomum bejolghota*	11	0.8
Ligusticum sinense	18	1.3	*Carthamus tinctorius*	11	0.8
Angelica sinensis	18	1.3	*Aquilaria crassna*	10	0.7
Foeniculum vulgare	17	1.3	*Tinospora crispa*	10	0.7
Dracaena loureiroi	17	1.3	*Cinnamomum bejolghotha*	10	0.7
Artemisia annua	17	1.3	*Curcuma zedoaria*	10	0.7
Terminalia chebula	16	1.2			

Source: Analysis based on prescriptions written for treating female infertility in TTM historical textbooks.

4. Frequency analysis of TTM herbal types used for female infertility treatment in Thai Patients

The most frequently prescribed TTM herb properties are hot tasting herbs (51.8%), followed by cold tasting herbs, and finally mild tasting herbs. See Table 4.

Table 4 Frequency of TTM herb types prescribed to Thai patients for the treatment of female infertility

Herbal properties	Frequency	Frequency rate (%)
Hot taste	694	51.8
Cold Taste	338	25.2
Mild Taste	307	22.9

Source: Analysis based on prescriptions written for treating female infertility in TTM historical textbooks.

5. Association analysis.

5.1 Association analysis of TCM prescriptions

Several important herb/drug combinations were identified in the association analysis for TCM herbal prescriptions, which are: *Curculigo orchioides - Epimedium brevicornum*; *Bupleurum chinensis - Dry human placenta - Cuscuta chinensis - Morus alba*; *Dry human placenta - Epimedium brevicornum - Cuscuta chinensis - Morus alba.* See table 5.

Table 5 Key associations of Chinese herbal medicines prescribed for the treatment of female infertility in Thailand.

Consequent	Antecedent	Support %	Confidence %	Lift
Curculigo orchioides	*Epimedium brevicornum*	0.457	0.953	1.648
Cuscuta chinensis	*Morus alba*	0.453	0.944	1.967
Bupleurum chinensis Dry human placenta	*Cuscuta chinensis*	0.300	0.957	1.995
Bupleurum chinensis Dry human placenta	*Morus alba*	0.309	0.986	2.054
Dry human placenta *Cuscuta chinensis*	*Morus alba*	0.363	0.988	2.059
Dry human placenta) *Epimedium brevicornum*	*Morus alba*	0.323	0.960	2.001
Atractylodes macrocephala *Morus alba*	*Bupleurum chinensis*	0.305	0.944	2.241
Bupleurum chinensis *Cuscuta chinensis*	*Morus alba*	0.327	0.986	2.056
Bupleurum chinensis *Morus alba*	*Cuscuta chinensis*	0.327	0.948	1.976
Atractylodes macrocephala *Cuscuta chinensis*	*Morus alba*	0.300	0.971	2.024
Cuscuta chinensis *Curculigo orchioides*	*Morus alba*	0.309	0.986	2.054
Cuscuta chinensis *Curculigo orchioides*	*Epimedium brevicornum*	0.305	0.971	1.679
Morus alba *Curculigo orchioides*	*Epimedium brevicornum*	0.318	0.973	1.681
Lycium babarum *Curculigo orchioides*	*Epimedium brevicornum*	0.323	0.973	1.682
Pseudostellaria heterophylla *Curculigo orchioides*	*Epimedium brevicornum*	0.359	0.964	1.666
Lycium babarum *Morus alba*	*Cuscuta chinensis*	0.368	0.965	2.011
Epimedium brevicornum *Cuscuta chinensis*	*Morus alba*	0.386	0.977	2.037
Bupleurum chinensis Dry human placenta *Cuscuta chinensis*	*Morus alba*	0.300	1.000	2.084
Bupleurum chinensis Dry human placenta *Morus alba*	*Cuscuta chinensis*	0.300	0.971	2.024
Dry human placenta	*Morus alba*	0.314	1.000	2.0

Consequent	Antecedent	Support %	Confidence %	Lift
Epimedium brevicornum *Cuscuta chinensis*				84

5.2 Association analysis of TTM prescriptions

Several important herb/drug combinations were identified in the association analysis for TTM herbal prescriptions, which are: *Atractylodes lancea* - *Angelica dahurica*; *Piper sarmentosum- Zingiber officinale* - *Piper retrofractum*; *Piper sarmentosum* - *Piper interruptum* - *Zingiber officinale* - *Piper retrofractum*; *Piper sarmentosum* - *Piper interruptum* - *Plumbago indica* - *Zingiber officinale*. See table 6.

Table 6 Results of association rules for TTM herbal used for female infertility (n=56); herb names are in Latin

Consequent	Antecedent	Support %	Confidence %	Lift
Piper sarmentosum	*Plumbago indica*	0.282	0.923	2.378
Atractylodes lancea	*Angelica dahurica*	0.212	1.000	3.864
Ligusticum sinense	*Angelica sinensis*	0.200	0.944	4.460
Cuminum cyminum	*Nigella sativa*	0.224	0.864	2.097
Piper sarmentosum , *Piper interruptum* ,	*Plumbago indica*	0.247	0.913	2.352
Piper sarmentosum, *Piper interruptum*	*Piper retrofractum*	0.247	0.913	1.617
Piper retrofractum, *Piper sarmentosum*	*Piper interruptum* ,	0.247	0.913	2.874
Piper retrofractum, *Piper interruptum* , Piper ribesoides	*Piper sarmentosum*	0.247	0.913	2.985
Piper sarmentosum, *Zingiber officinale*	*Plumbago indica*	0.212	0.947	2.440
Piper retrofractum, *Piper sarmentosum*	*Plumbago indica*	0.247	0.913	2.352
Piper sarmentosum, *Zingiber officinale*	*Piper retrofractum*	0.224	1.000	1.771
Piper retrofractum, *Piper sarmentosum*	*Zingiber officinale*	0.224	0.826	1.463
Piper interruptum , *Zingiber officinale*	*Plumbago indica*	0.224	0.950	2.447
Piper interruptum , *Plumbago indica*	*Piper retrofractum*	0.247	0.840	1.488
Piper retrofractum, *Piper interruptum*	*Plumbago indica*	0.247	0.913	2.352
Piper retrofractum, *Plumbago indica*	*Piper interruptum*	0.247	0.840	2.644
Piper interruptum , *Piper ribesoides*, *Zingiber officinale*	*Piper retrofractum*	0.224	0.950	1.682
Piper sarmentosum, *Zingiber officinale*, *Plumbago indica*	*Piper retrofractum*	0.224	0.905	1.602
Piper retrofractum, *Piper sarmentosum*, *Piper interruptum* ,	*Plumbago indica*	0.224	0.905	2.330
Piper retrofractum, *Piper sarmentosum, Plumbago indica*	*Piper interruptum*	0.224	0.905	2.848

Consequent	Antecedent	Support %	Confidence %	Lift
Piper retrofractum, Piper interruptum , Plumbago indica	*Piper sarmentosum*	0.224	0.905	2.958
Piper sarmentosum, Piper interruptum , Zingiber officinale	*Piper retrofractum*	0.200	1.000	1.771
Piper sarmentosum, Piper interruptum , Plumbago indica	*Piper retrofractum*	0.212	1.000	1.771
Piper retrofractum, Piper sarmentosum, Piper interruptum ,	*Plumbago indica*	0.212	0.857	1.518
Piper retrofractum, Piper sarmentosum, Piper interruptum ,	*Plumbago indica*	0.212	0.947	2.440
Piper retrofractum, Plumbago indica, Zingiber officinale	*Piper sarmentosum*	0.212	0.857	2.802
Piper interruptum , Plumbago indica, Zingiber officinale	*Piper retrofractum*	0.212	0.947	1.678
Piper retrofractum, Piper interruptum , Plumbago indica	*Zingiber officinale*	0.212	1.518	0.857
Piper retrofractum, Piper interruptum , Piper ribesoide, Zingiber officinale	*Plumbago indica*	0.212	0.947	2.440
Piper retrofractum, Plumbago indica, Zingiber officinale	*Piper interruptum*	0.212	0.857	2.698

6. Theoretical comparison of TCM and TTM in the treatment of female infertility

Both TCM and TTM have a long history, dating back several thousand years. According to the records in historical texbooks, the female infertility treatment theory was first seen over 2,000 years ago in "Huangdi Neijing". Female infertility in TCM has been substantially researched in terms of theory, clinical efficacy, and safety, and it is constantly developing. Traditional Chinese medicine is becoming more important in the treatment of female infertility. The development of TTM corresponds with the developmental history of Thailand. Since 273 BC, ancient Indian medicine entered Thailand and the traditional medical culture at that time was combined with local medical theory to form the basis of modern day system of Thai traditional medicine. The principles, methods, prescriptions of Thai medicine for treating female infertility are mainly found in “Prathomjinda”, “Thartwiphang”, “Maha Chotirat”; in particular, “Maha Chotirat” is the most important ancient book on the treatment of women's miscellaneous diseases.

6.1 Mechanism of Pregnancy in TCM and TTM

Traditional Chinese medicine explains the conditions of pregnancy as mainly the age at which the kidney essence of both male and female are full and ready for reproduction (Tiangui) , the qi and blood of women are full and smooth, yin and yang are balanced, and after intercourse, conception will be possible. It is pointed out that being full of kidney essence and sufficient and smooth qi and blood are the important conditions for getting pregnant in TCM theory. Thai traditional medicine explains that there are two important conditions needed in order to successfully conceive, which are: 1) the woman has a regular menstruation cycle, sufficient blood, and a normal uterus; and 2) couples have proper intercourse condition.

Based on the literature, TCM and TTM have similar theories on getting pregnant, which are based on two main conditions: 1) "sufficient blood, normal menstruation"; and 2) "men and women should have proper sex". Differences between TCM and TTM is that a key condition in TCM requires "the kidney essence and smooth and sufficient qi, and the balancing of yin and yang", while a key condition in TTM is a "normal uterus".

6.2 Etiology and pathogenesis of female infertility in TCM and TTM

Traditional Chinese medicine and Thai traditional medicine similarly explain the etiology of female infertility. For congenital and pathogenic etiology, TCM will focus on the "5 abnormalities" of the female reproductive system. If any of the five abnormalities are present, medication will be an ineffective treatment for female infertility. Congenital etiology of female infertility in TTM are genetic issues that cause amenorrhea or a light blood flow during menstruation. The two most common pathogeneses of female infertility in traditional Chinese medicine are kidney deficiency and spleen deficiency, both of which cause a deficiency in qi and blood and affects the uterus and *Chong Ren* meridians. Kidney and spleen deficiencies can also cause liver qi stagnation, blood stasis, internal phlegm, and dampness, which can prevent the uterus from functioning properly, and thereby causing infertility. In traditional Thai medicine, the pathogenesis of female infertility is insufficient blood, an irregular menstrual cycle, and abnormal changes in the uterus.

Thus, TCM and TTM have common pathogenesis etiology for female infertility. They both focus on the woman's blood, menstruation, and health of the uterus. The difference was just in their specific theoretical understanding.

Additionally, both TCM and TTM point to similar unhealthy lifestyle factors as contributing factors of female infertility, such as an improper diet, being overworked, being excessively emotional, and so on. However, there are some differences as well. For example, in traditional Chinese medicine, anger can damage the liver, but in Thai traditional medicine, anger reduces the blood level.

6.3 Treatment principles and methods

Based on the main treatment principles of both TCM and TTM for female infertility, the common important treatment principle is "treatment aiming at the condition's pathogenesis". Traditional Chinese medicine treatment based on "syndrome differentiation" focuses on warming and nourishing the kidney's yang, nourishes qi and blood, soothing liver and regulating qi, promote blood circulation and remove blood stasis, dry dampness, and reduce phlegm. Thai traditional medicine has a similar holistic view as TCM. The treatment methods used in TTM are based on etiology and pathogenesis of the individual patient and also focuses on relevant factors such as age, living conditions, and so on; the main treatment focuses on regulating menstruation, balancing and nourishing the body's four elements, nourishing the blood, promote blood circulation and remove blood stasis, eliminate bad blood, and blood detoxification.

6.4 The prevention and care theory

Both TCM and TTM encourage a healthy lifestyle and having a proper diet are important factors in preventing female infertility. In Traditional Chinees medicine, greasy products, and alcohol consumption should be minimized to avoid spleen deficiency that can produce phlegm-dampness inside the body and causes insufficient blood and qi production. In Thai traditional medicine, it is suggested that foods that are too spicy be avoided because they cause blood deficiency, and that a person's diet should focus on nourishing the body's four elements.

Both TCM and TTM agree that mental health and emotional regulation are important to preventing infertility; both mention “peace of mind”. In TCM, emotions can be regulated using herbal medication and exercise. In TTM, the use of meditation to promote peace of mind. Peace of mind is related to the normal function of the liver, spleen, and kidney in TCM, and is related to blood sufficiency in TTM. An appropriate sexual condition is also important to mental health. Excessive sexual activity, or inappropriate sex conditions cause kidney essence yin and yang deficiencies according to TCM, and cause blood deficiency in TTM. Therefore, both TCM and TTM encourage properly engaging in sexual intercourse and having a calm mind during intercourse, which can nourish the blood and prevent infertility.

7. The prescription rules and pattern of TCM and TTM for female infertility treatment

7.1 Discussion on the overall prescription and compatibility of traditional Chinese medicine for the treatment of infertility in Thai female patients

According to the analysis of TCM prescriptions, it was suggested that Dr. Zheng's basic herbal types used structure for the treatment of female infertility in Thailand and follows: “nourishing group – heat clearing group – blood circulation promotion and removal of blood stasis group - treatment exterior symptoms group”. The reason of using exterior symptoms treatment herbs, *Bupleurum chinensis, Mentha Canadensis,* because both were related to liver meridian and it was used for soothing and regulating liver qi in the prescriptions. The data mining analysis showed the herbs used with thigh highest frequency wer *Pseudostellaria heterophylla, Eucommia ulmoides, Epimedium brevicornum, Astragalus membranaceus, Lycium barbarum, Cuscuta chinensis, Morus alba, Curculigo orchioides, Atractylodes macrocephala, Glycyrrhiza uralensis, Bupleurum chinensis,* dry human placenta, *Rehmannia glutinosa, Sedum sarmentosum, and Paeonia lactiflora*. According to the drug association analysis that is based on data mining, the highest herbal compatibility were “ *Curculigo orchioides - Epimedium brevicornum*”, and “*Bupleurum chinensis - d*ry human placenta - *Cuscuta chinensis - Morus alba - Epimedium brevicornum* ”. It can be concluded that Dr. Zheng's prescription for the treatment of female infertility in Thailand is based on the TCM treatment path for female infertility to nourish qi and blood, warm and tonify kidney-Yang, regulate Chong and Ren meridians, disperse the liver qi stagnation, promoting blood circulation and remove blood stasis.

7.2 The prescription and compatibility of TTM herbal used for female infertility

Based on the analysis of TTM prescriptions, the most important compatibility in prescriptions were the combination of spicy and hot taste herbs. Based on TTM theory, spicy and hot herbs are mainly used in the rainy season, when the humidity is high and the body is easily exposed to cold and dampness. This might indicate that the prescriptions were mainly used in women with a cold body type. If “wind element type” of herbs are used, it might indicate that most cases of female infertility are among patients that are more than 30 years old; after the age of 30, internal organs begin to lose some function, including the reproductive function. If pungent tasting herbs are used to nourish the fire element in the body, which emphasizes that female infertility is more common in patients with a cold constitution. In addition, pungent tasting herbs are also used to regulate the body’s 4 elements, promoting blood circulation, and regulating the menstrual cycle. The data showed that “neutral nature” herbs had the highest frequency in prescriptions, which emphasize that nourishing the blood was one of the most important treatments.

The analysis of drug associations based on data mining showed the highest herbal compatibility were “*Atractylodes lancea - Angelica dahurica”* which is mainly for nourishing

blood, and regulating and nourishing the body's 4 elements. The second important herbal compatibility were "*Piper sarmentosum - Piper interruptum - Zingiber officinale - Piper retrofractum - Plumbago indica"*. These spicy and hot nature herbs were called "Benchakun" prescriptions, which mainly regulate the body's wind element, nourish the body's 4 elements, and regulate blood.

Discussion

1. Similarities and differences between TCM and TTM on their therapeutic theories for the treatment of female infertility.

The results show TCM and TTM have the three factors in common that are necessary for conception: patient must have sufficient nourishment from their blood, have a normal menstrual cycle and flow, and have appropriate sexual conditions. Traditional Chinese medicine has two additional factors, which are kidney essence and Qi, and the balance of yin and yang. On the other hand, Thai traditional medicine also includes a healthy condition of the uterus as an important factor.

There are similar principles in both TCM and TTM explaining female infertility. Factors causing female infertility are categorized into congenital factors and the secondary factors. For congenital factors, TCM discusses the 5 abnormalities of the female reproductive system, and TTM points to inherited blood disorders. Traditional Chinese medicine and Thai traditional medicine have common explanations on the secondary factors. For example, lifestyle and environmental factors, including bad diet, lifestyle, excessive emotions, excessive sexual activity, or inappropriate sex conditions. Similar to TCM, which describes exogenous pathogenicity (wind, cold, dampness), TCM also points to woman's age as well as the time of year which can also be important factors.

The disease mechanism: TCM mainly explains "deficiency of kidney and spleen pattern" and "stagnation pattern" that cause deficiency of Qi and blood, the imbalance of Cong and Ren meridians, the stagnation of uterus and uterus meridian, and so on. In TTM, it is mainly explained that the deficiency of blood, irregular menstruation, and blood stasis, blood clot, and the abnormal uterus function were the main mechanism of infertility. The treatment analyzed result showed both TCM and TTM were based on disease mechanisms and a holistic diagnosis pattern, then choose the appropriate treatment option: for the treatment theory we found that period regulation, nourishing blood, regulate and treat uterine diseases, improve the body circulation, and remove the pathological waste were the common treatments, but further treatment theory on TCM were to warm and tonify the kidney-Yang, disperse the liver Qi stagnation, eliminating phlegm and dampness, and TTM mainly regulate the 4 basic body elements, warm the fire element.

2. Similarities and differences between TCM and TTM on their prescription compatibility pattern in the treatment of Thai female infertility.

The data mining results showed 162 unique herbs were used from 223 TCM prescriptions, TCM's most frequency used in the prescription herbs were *Pseudostellaria heterophylla*, *Eucommia ulmoides*, *Epimedium brevicornum*, *Astragalus membranaceus*, *Lycium babarum*, *Cuscuta chinensis*, *Morus alba*, *Curculigo orchioides*, *Atractylodes macrocephala*, *Glycyrrhiza uralensis*, *Bupleurum chinensis*, Dry human placenta, *Sedum sarmentosum*, *Paeonia lactiflora* (see table 1); TCM's most important compatible prescription herbs were "*Bupleurum chinensis* - Dry human placenta, *Cuscuta chinensis* - *Morus alba* - *Curculigo orchioides* - *Epimedium brevicornum*" , so the TCM treated Thai female infertility prescription compatibility rules were to nourish Qi and blood, warm and tonify kidney-Yang,

regulate Chong and Ren meridians, disperse the liver Qi stagnation, promoting blood circulation and remove blood stasis; 229 herbal were used from 85 TTM prescriptions, *Piper retrofractum*、*Zingiber officinale*、*Piper nigrum*、*Plumbago indica*、*Piper interruptum*、*Piper sarmentosum*、*Myristica fragrans*、*Angelica dahurica*、*Atractylodes lancea*、*Ligusticum sinense*、*Angelica sinensis*、*Artemisia annua*、*Cuminum cyminum*、*Nigella sativa*、*Foeniculum vulgare*、*Lepidium sativum*、*Syzygium aromaticum*、*Cyperus rotundus*、*Dracaena loureiroi*、*Terminalia chebula* were the most frequently used herbs in the prescription (see table 2); "*Atractylodes lancea - Angelica dahurica*", "*Piper sarmentosum - Piper interruptum - Zingiber officinale - Piper retrofractum - Plumbago indica*" were the most compatible found, so TTM prescription compatibility rules were to regulate and nourish the 4 basic body elements, nourish blood, nourish the fire element to eliminate cold inside body, eliminate blood stasis, and treat all other blood disorders .

Conclusion

1. There are similarities between TCM and TTM in their diagnosis and therapeutic approaches to treat female infertility, but there were differences on the explanation of some principles.

2. Traditional Chinese medicine's and Thai traditional medicine's diagnosis are based on a holistic view, and most of the Thai female infertility patients had the "cold and deficiency pattern", then main prescription pattern compatibility of regulate menstrual cycle and flow, nourishing blood, regulate and treat the uterine diseases, improve body circulation, and to remove the blood stasis might be the effective compatible prescription. But there were differences on the specific herbal used that rely on their medicinal theories.

Due to the research on the treatment on female infertility in Thailand is limited, further research is still needed.

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