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A Scoping Review: Efficacy of Medical-Grade Honey as an Alternative Therapy against Vulvovaginal Candidiasis

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Abstract

Background: The emerging of non-*albicans Candida* species and *Candida* species have becoming potential clinical pertinence among numerous patients with vulvovaginal candidiasis. Routine treatment option include fluconazole as a primary therapeutic choice for the management of both recurrent and vulvovaginal candidiasis. However, concomitant increase in both acquired and inherent resistance of fluconazole against the diseases have been reported. Medical-Grade Honey has immunomodulatory, protective and antimicrobial activity that constitutes a reputed alternative treatment against *Candida* species mediated vaginal infections.

Aim: This study examined the efficacy of Medical-Grade Honey against vulvovaginal candidiasis compared to fluconazole therapy.

Method: This study examines the *in vitro* studies of the potency of Medical-Grade Honey against vulvovaginal candidiasis.

Results: The study showed that Medical-Grade Honey is more effective against vulvovaginal candidiasis compared to fluconazole that have positive effect on *Candida* species and antimicrobial activity. The synopsis of *in vitro* studies evaluating the antimicrobial activity of Medical-Grade Honey against *Candida* species showed that *Candida albicans* had the highest percentage frequency of 34.48% (10.00). The rate of antimicrobial activity of the substrate on different clinical isolates revealed that the substrate 8 (Local produced honey) have potential antimicrobial activity on *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei*, *Candida kefyr* and *Candida dubliniensis* with the percentage frequency of 20.69% (6.00). The lower limit of Minimum Inhibitory Concentration (MIC) value of different substrates revealed that the substrates 6 (Monofloral lavender honey) had the lowest MIC value with percentage frequency of 4.65% (16.00). The upper limit of MIC value of different substrates revealed that the substrate 5 (Honey and Miconazole) had the highest MIC value with percentage frequency of 14.78% (80.00).

Conclusion: From the reported *in vitro* studies, Medical-Grade Honey especially Monofloral Lavender Honey can be used against vulvovaginal candidiasis due to present of high fluconazole resistance rate issues. Monofloral Lavender Honey inhibit the growth of all *Candida* species and has the lowest minimum inhibitory concentration (MIC) which indicated that the honey is more effective as antifungal agents against the disease. Medical-Grade Honey has proven the effectiveness of immunomodulatory, protective, antimicrobial activity and can serve as alternative therapy against vulvovaginal candidiasis. This study suggest further *in vivo* analysis to confirm the effectiveness of Medical-Grade Honey against the disease.

Keywords: *Candida Species; Fluconazole; Vulvovaginal Candidiasis; In Vitro Studies; Medical-Grade Honey; In Vivo Analysis*

Introduction

Medical-Grade Honey (MGH) is highly potent in chronic and acute wound infections, rapid decrease of wound healing time, cost-effective, decreases pain, has anti-inflammatory activity, provides rapid wound contraction and epithelization, stimulates debridement and resolves numerous fungal ailments [1]. Vulvovaginal candidiasis is an awfully recurrent mucosal ailment of the lower reproductive tract of women, predominantly caused by the polymorphic opportunistic fungus such as *Candida albicans* and some facultative anaerobic bacteria such as *Gardnerella vaginalis*. Recently, according to statistics, yeasts are the second predominant of genital infections [2]. Among every ten females, seven suffer from vaginitis [3]. Every year, more than 9 million women were often referred to the specialists for proper management of the disease [4]. Frequent increase of diseases across the continents resulted to imposing about 1.8 USD to medical expenses. In vulvovaginal cases, a stinking and clumpy white discharge is considered to be a symptomatic of the infection [5]. Infected women usually faced challenges such as failure to carry on with their essential physical activities, loss of self-esteem and confidence, depression and anxiety, perplexity with their intimate relationships and sexual life [6]. With reference to global annual prevalence of 3871 per 100,000 women, recurrent vulvovaginal candidiasis affects more than 130 million women annually across the continents [6]. It was evaluated that highest prevalence of the disease is commonly observed in females of an age between 25 to 35 years old. Apparently, number of women infected with *candida* vulvovaginitis will increase to about 158 million patients by 2030 [7]. In Iran, more than 45% of women infected with *candida* vulvovaginitis [8]. It was evaluated that more than 70% of women were infected with the diseases of at least once in their lifetime whereas more than 40% of women are at risk of recurrence of *candida* vulvovaginitis [2]. More than 85% of vulvovaginal cases are predominantly caused by *Candida* species [9]. The disease is not a life threatening, but it can cause serious of mental, sexual and physical adverse effects. *Candida* vulvovaginitis was predicted to be a serious public health problem [10]. The predisposed factors of the disease include patients under antibiotic treatment, pregnant women, patients with acquired immunodeficiency syndrome (AIDS), women who take oral contraceptive pills concomitantly with high estrogenic, diabetic patients and patients with immune impairments [2]. The symptoms of disease include general uneasiness, itching, vaginal secretion, burning urination, dyspareunia, swelling, dysuria and painful [11]. *Candida* vulvovaginitis is commonly diagnosed based on history of infections because genital examination is burdensome to identify the specific organism due to disability of conventional methods [12]. Azole drugs are commonly taken as the first treatment line systematically sometimes with topical agents. However, some women may suffer from adverse effects of the prescribed therapy [3]. Ineffectiveness of the treatments, fungal resistance against azoles and the adverse effects of antifungal drugs resulted to a novel discovery of new antifungal drugs with insignificant challenges [2]. Honey contains oligosaccharides, glucose oxidase, catalase, hydrogen peroxide and low acidity level which are the most significant antimicrobial agents that inhibit intracellular metabolic pathway. In addition, nectar, organic acid, lysozyme, beeswax, propolis and pollen are also important chemical factors that provide antimicrobial properties to honey [13]. The antifungal activity of honey at first place, is due to hydrogen peroxide obtained from glucose, oxygen from glucose oxidase enzyme [2]. Honey is very potent in the treatment of burns, inflammation, wounds and stratum corneum wounds [14]. When taken probiotic vaginal capsule like *lactobacillus* directly in vagina of women who were infected with *Candida* vulvovaginitis for at least 5 days, it would enhance the treatment level of the infection for more than 90% against quantity of 83% placebo and concluded that the existing *lactobacillus* in substrate may distort the growth of fungus in vagina of women infected with vulvovaginal candidiasis by producing metabolites such as hydrogen peroxides and acid medium [53]. Using honey in culture medium with *Candida* vulvovaginitis for at least 2 hours it inhibited the growth of *Candida* species. Women who often consumed honey, shows drastically reduction in the treatment of the disease [15]. The symptoms of the disease is determined by the interaction between *Candida* virulence factors and *Candida* species, inflammatory status, *Lactobacilli* population, oxidative stress, estrogen and host immunity. Instability of any of these factors may instigate the recurrent of the disease [16]. Apparently, there is an increase in resistance of fungal species towards current and available antifungal agents. An urgent need for alternative therapies of the disease and to preclude its recurrence is highly needed. It is paramount to know more about the causative agents of vaginitis, the different therapies options and their effectiveness to understand how novel treatments could improve the quality of life and clinical success.

Materials and Methods

This study follow the techniques proposed by Cooper [17] and Moher., *et al*. [18] through assessing, selecting and evaluating the sources of information, integrating and analyzing the results of the studies. And follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommended by PRISMA.

Selecting the sources of information

A search for studies that includes, Medical-Grade Honey, Honey, Antifungal drugs, Fluconazole, Vulvovaginal candidiasis, *Candida* species and Fungal species from January 2022 to May 2022 was conducted in databases that include indexed journals, journals that publish natural and pharmaceutical new therapy against Vulvovaginal candidiasis and the studies cited in each of the articles selected for this study were also searched again. In the search for information, only English keywords were used. The databases evaluated were Ecronicon, Scopus, Science Direct, Web of Science, Scielo and the publications from all years included in the databases were analyzed. In the article search, the following keywords were used: medical-grade honey AND vaginitis, honey AND vulvovaginal candidiasis, fluconazole AND fungal pathogens, fluconazole AND candidiasis, honey AND antifungal drugs, new therapy AND vaginitis, and effective treatment AND vulvoviginitis.

Statistical analysis

Descriptive statistics (Frequency and percentage) of clinical isolates, substrates used against clinical isolate, lower and upper limit of minimum inhibitory concentration (MIC) from *in vitro* studies were enumerated and subjected to graphic profile using IBM® SPSS® Statistics version 25.0 (IBM® Corp., Armonk, NY, USA).

Results

Of the 109 articles reviewed, only 53 are reviewed systematically based on the efficacy of anti-inflammatory, antimicrobial, anti-oxidative and immunomodulatory activity of Medical-Grade Honey against vulvovaginal candidiasis. Table 1 showed the *in vitro* efficacy of antimicrobial activity of Medical-Grade Honey and fluconazole. The results revealed that Medical-Grade Honey have the potential positive effect on all attributes associated with vaginal candidiasis such as Non-*albicans Candida* species, *Candida* species, antimicrobial activity, biofilms, antioxidative activity, increased resistance, anti-inflammatory activity, vaginal mucosal response, osmotic activity and pH and without negative effect related to antipathogenic activity while fluconazole have positive effect on *Candida* species and antimicrobial activity and had negative effect on Non-*albicans Candida* species, biofilms, antioxidative activity, increased resistance, anti-inflammatory activity, vaginal mucosal response, osmotic activity and pH. Table 2 revealed the *in vitro* studies of the antimicrobial activity of Medical-Grade Honey against *Candida* species. Figure 1 showed the rate of occurrence of clinical isolates from the reported studies. The results showed that *Candida albicans* had the highest percentage frequency of 34.48% (10.00) followed by *Candida glabrata* with 17.24% (5.00). Figure 2 showed the rate of antimicrobial activity of the substrate on different clinical isolates. The results revealed that substrate 8 (Local produced honey) had the highest potential antimicrobial activity with the percentage frequency of 20.69% (6.00) compared to other substrate. Figure 3 showed the lower limit of Minimum Inhibitory Concentration (MIC) value of different substrates. The results revealed that substrate 6 (Monofloral lavender honey) had the lowest MIC value with percentage frequency of 4.65% (16.00) followed by substrate 9 (Jarrah, Medihone, Comvita and artificial honey) with 5.23% (18.00). Figure 4 showed the upper limit of MIC value of different substrates. The results revealed that the substrate 5 (Honey and Miconazole) had the highest MIC value with percentage frequency of 14.78% (80.00) followed by substrate 10 (Honey, Beewax and Olive oil mixture) with 12.19% (66.00).

S/N	Attribute	Medical-Grade Honey (MGH)	Fluconazole	Control	Reference
1	Non-*albicans Candida* species	MGH have demonstrated the susceptibility profile against *Candida dubliniensis*, *Candida tropicalis*, *Candida kefyr*, *Candida glabrata* and *Candida parapsilosis* which could fulfill the promising demand for new antifungal agents against *Candida* infections.	Vulvovaginal candidiasis caused by non-*albicans Candida* species is frequently increasing due to misuse or overuse of fluconazole therapy. The disease are less susceptible to azoles and more commonly resistant.	Not reported	Berkow and Lockhart, [44] Peyton., *et al.* [59] Eteraf-Oskouei and Najafi, [13] Riel., *et al.* [19] Aboushady., *et al.* [57] Irish., *et al.* [27] Cater AD., *et al.* [58] Mahl., *et al.* [60] Steel., *et al.* [61]
2	*Candida* species	MGH at lower and higher concentration inhibited the growth of *Candida* species at the intermediate level, concentration of 80% had the highest inhibitory effect and produced a high clinical and mycological cure rate in women with vulvovaginal candidiasis as compared to other antifungal agents.	Fluconazole is commonly active against primary fungal pathogens and yeasts but inactive against filamentous fungal infection. Fluconazole can be used to treat deep mycosis infection, esophageal or oropharyngeal candidiasis and disseminated candidiasis. The adverse effects observed from taking fluconazole was generally mild.	Not reported	
3	Antimicrobial activity	Honey had antifungal activity on fluconazole-resistance strains evaluated in culture media containing different concentration.	Fluconazole inhibits the cytochrome P450 enzyme lanosterol demethylase in the ergosterol biosynthesis pathway. This distorts the activations of oxygen and the process of ergosterol biosynthesis. Ergosterol is a significant agent of fungal cell membranes, this inhibition is toxic and cell grow is arrested.	Not reported	
4	Biofilms	MGH disrupts cellular components and inhibit the formation of biofilms by a broad range of pathogenic organisms and can distort the established biofilms and kill resident cells.	The biofilm formation in the pathogenesis of vulvovaginal candidiasis generates increased resistance and virulence towards fluconazole. Biofilm are less sensitive to distort by the host immune system and higher resistance profile of biofilms compared to the planktonic components has been reported. Presently, no therapy targets *Candida* biofilm formation and eradication which make biofilms a potential clinical issue that urgently demands novel treatment options.	Not reported	
5	Antioxidative activity	The phenolic compounds present in MGH exhibit anti-inflammatory, anti-carcinogenic, analgesic activities, antiatherogenic, immune modulating and antithrombotic. Compounds such as flavonoids, phenolic acid, peptides, ascorbic acid, maillard reaction products, tocopherols, reduced glutathione, superoxide dismutase and catalase working together to provide a synergistic antioxidant effect.	Fluconazole therapy cause oxidative damage in DNA. Possible participation of reactive oxygen species as organic peroxides and O_2 in antifungal mechanism of fluconazole which leads to high glutathione peroxidase and superoxide dismutase enzymatic activities and oxidative DNA damage in *Candida* species.	Not reported	

6	Increased resistance	MGH formulation is significantly reduced the growth of *Candida* species in a dose-dependent manner and has a strong antifungal activity against *Candida* species without any adverse effect.	Fluconazole is not fungicidal but fungistatic, there is an increased opportunity to develop acquire resistance in the present of this antifungal agent. There are some challenges in fluconazole therapy such as increase in antifungal resistance, existence of biofilms and vulvovaginal candidiasis caused by non-*albicans Candida* species.	Not reported	
7	Anti-inflammatory activity	MGH is able to prevent inflammatory components, angiogenesis and showing effective inhibitory activities against PGE_2 and $TNF_{-\alpha}$, prevent the activities of cyclooxygenase, improved epithelization, low glycosaminoglycan and proteoglycan components, less edema, better wound contraction, infiltration of fewer granular and mononuclear cells and necrosis, decrease in concentration of prostaglandins in plasma, reduce the inflammation and exudation, stimulates tissue regeneration, promotes healing and diminish scar size.	Anti-inflammatory potency of fluconazole in relation to molecular structure is less active compared to itraconazole, ketoconazole and voriconazole.	Not reported	
8	Vaginal mucosal response	The antioxidative and anti-inflammation properties of MGH can significantly modulates and benefit the vaginal environment even under inflammatory and fungal infection. Phytochemicals are present in the MGH which subsequently release free oxygen radicals, minimizing inflammation and tissue damage.	Despite fluconazole being effective to relieve or reduce the symptoms of vulvovaginal candidiasis, the antifungal agent does not have influence on the vaginal mucosal response and long term cure rate remain difficult to maintain and achieve.	Not reported	
9	Osmotic activity	*Candida* species are highly vulnerable to the osmotic effect of all honey.	Not like fluconazole, the sugar-rich composition of MGH has an osmotic activities that attracts fluid from the surrounding environment and results to dehydration and makes the *Candida* species vulnerable.	Not reported	
10	pH	pH of MGH is ranged from 3.2 – 4.5, is due to the organic acids such as citric acid, glutamic acid, malic and pyruvic acid and high sugar make honey inhibitory to microbial growth, and activity remains even when slightly diluted, produce hydrogen peroxide (H_2O_2) as a result of glucose oxidation.	*Candida* species in vagina apparently prefers a low pH to develop infection, acute vulvovaginal candidiasis may likely be associated with a disturbance of the vaginal microbiota and fluconazole therapy may lower the pH level and increase *Lactobacilli* species in patients with recurrent vulvovaginal candidiasis.	Not reported	

Table 1: *Synopsis of in vitro efficacy of antimicrobial activity between Medical-Grade Honey and Fluconazole against vulvovaginal candidiasis.*

S/N	Substrate	Clinical Isolates	Content	MIC	Efficacy	References
1	- Portuguese honey - Manuka honey	*Candida albicans* *Candida tropicalis* *Candida glabrata* *Candida parapsilosis*	Physiochemical properties of the substrates and antifungal activity in *Candida* species planktonic and biofilm assays	25 - 50% w/v	-All the substrates had a potent activity against *Candida* species -Biofilms can be reduced at a concentration of 50 - 75% honey	Fernandes., *et al*. [20]
2	-Mexican Yucatan honey -L-Mesitran soft	*Candida albicans*	Performing clinical trials for RVVS and alternative to available OTC fungistatic drugs	25 - 50%	-No effect of 40% of the substrate alone -The supplements in L-Mesitran enhaced the antimicrobial activity of the substrate formulation	Hermanns., *et al*. [7]
3	Iranian Honey	*Candida albicans* *Candida tropicalis* *Candida glabrata* *Candida krusei*	The antifungal activity of different honeys against 40 fluconazole (FLU) resistant *Candida* species	25 - 56.25% v/v	All tested honeys had antifungal activity against fluconazole resistant *Candida species*.	Shokri., *et al*. [21]
4	Jujube (Zizyphus spina-christi) Honey	*Candida albicans*	The in vitro inhibitory activity of the substrate against pre-formed biofilm and its interference with the biofilm formation of *Candida albicans*	40% w/v	The substrate has antifungal properties against *Candida albicans* and has the potential ability to inhibit the formation of *Candida albicans* biofilms and disrupt established biofilms	Ansari., *et al*. [22]
5	Honey and Miconazole	*Candida albicans*	The effect of substrates against *Candida albicans*, in vitro	80%	The honey prevented the growth of *Candida albicans* greatly and miconazole inhibited it completely.	Banaeian-Borujeni., *et al*. [23]
6	Monofloral lavender honey	*Candida albicans* *Candida krusei* *Crytococcus neoformans*	Effectiveness of the substrate against *Candida albicans*, *Candida krusei* and *Cryptococcus neoformans*	16 - 31% w/v	All the yeast growth were reduced in the present of honey. The substrate might be tapped as a natural resources to look for new medicines for the treatment of mycotic infections.	Estevinho., *et al*. [24]
7	Turkish Honey	*Candida albicans* *Candida glabrata* *Candida krusei* *Trichosporon* species	The activity of the substrate against yeasts at different concentration.	45 - 65% v/v	All of the yeast strains tested were inhibited by substrates	Koc., *et al*. [25]

8	Local Produced Honey	*Candida albicans* *Candida tropicalis* *Candida glabrata* *Candida krusei* *Candida kefyr* *Candida dubliniensis*	The anti-candidal activity of 28 locally produced substrates from two flora sources against some pathogenic *Candida* species	20 - 60% v/v	All substrates were able to produce complete inhibition of *Candida* growth with minimum fungicidal concentration	Khosravi., *et al.* [26]
9	-Jarrah honey -Medihoney -Comvita honey -Artificial honey	*Candida albicans* *Candida glabrata* *Candida dubliniensis*	Effectiveness of the substrates against clinical isolates of some *Candida species*	18 - 43% w/v	All of the isolates were inhibited by substrate and effective against isolates who were resistance to itraconazole or/and fluconazole	Irish., *et al.* [27]
10	Honey, beeswax and Olive oil mixture	*Candida albicans* *Staphylococcus aureus*	The effect of the substrates on the growth of *Candida albicans* and *Staphylococcus aureus* isolated from human specimens	50 - 66% v/v	The amount of substrates in mixture were completely inhibited the growth of *Candida albicans* and *Staphylococcus aureus*	Al-Waili., *et al.* [28]

Table 2: *Synopsis of in vitro studies evaluating the antimicrobial activity of Medical-Grade Honey against Candida species.*

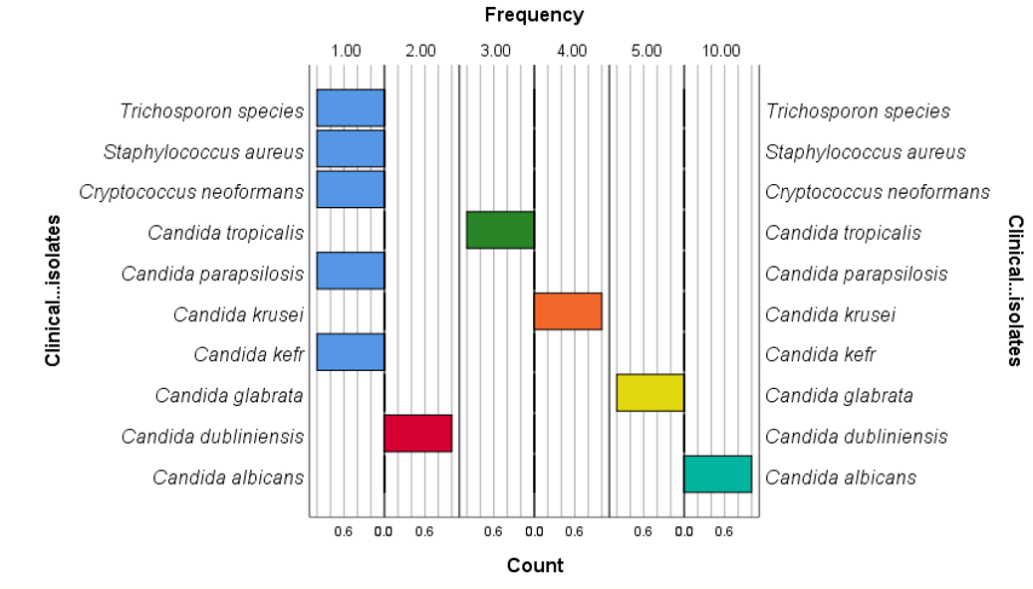

Figure 1: *Frequency of the clinical isolates reported from in vitro studies.*

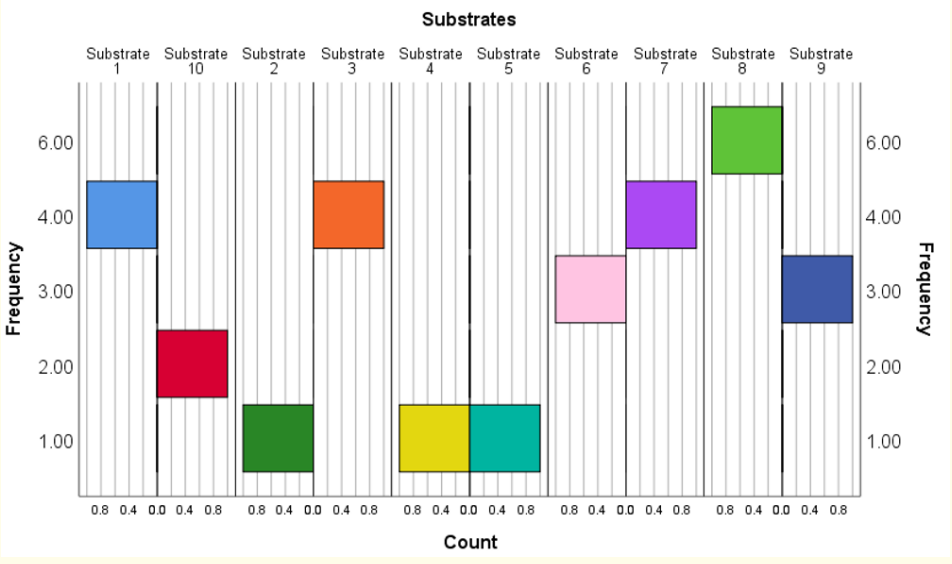

Figure 2: *Frequency of substrates against clinical isolates.*

Substrate 1: Portuguese honey, Manuka honey; Substrate 2: Mexican Yucatan Honey, L-Mesitran soft; Substrate 3: Iranian Honey; Substrate 4: Jujube (Zizyphus Spina-christi) Honey; Substrate 5: Honey and Miconazole; Substrate 6: Monofloral lavender Honey; Substrate 7: Turkish Honey; Substrate 8: Local Produced Honey; Substrate 9: Jarrah Honey, Medihoney, Comvita Honey, Artificial Honey; Substrate 10: Honey, Beeswax and Olive oil mixture.

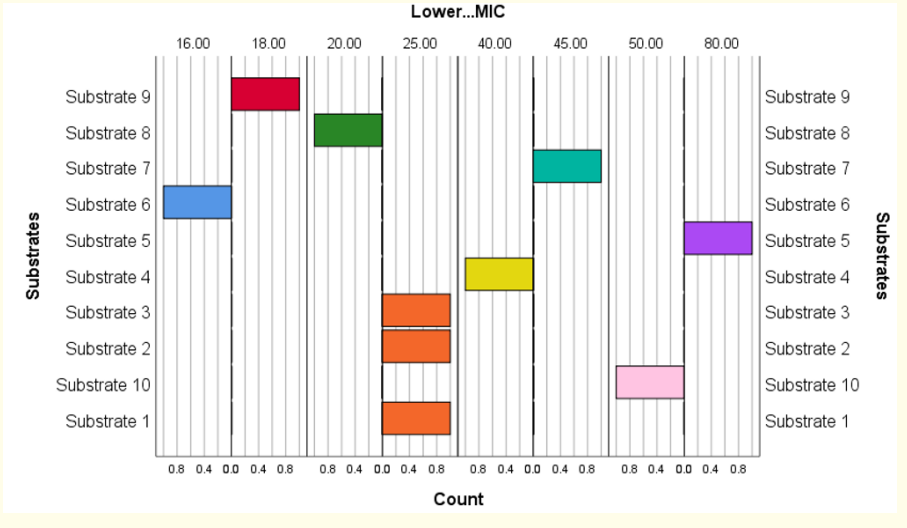

Figure 3: *Evaluation of the lower limit of MIC from all substrates.*

Substrate 1: Portuguese honey, Manuka honey; Substrate 2: Mexican Yucatan Honey, L-Mesitran soft; Substrate 3: Iranian Honey; Substrate 4: Jujube (Zizyphus Spina-christi) Honey; Substrate 5: Honey and Miconazole; Substrate 6: Monofloral lavender Honey; Substrate 7: Turkish Honey; Substrate 8: Local Produced Honey; Substrate 9: Jarrah Honey, Medihoney, Comvita Honey, Artificial Honey; Substrate 10: Honey, Beeswax and Olive oil mixture.

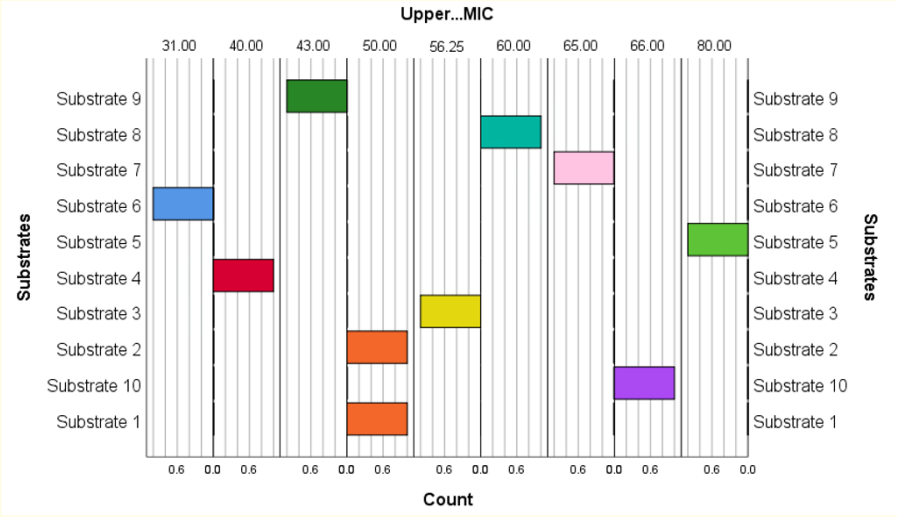

Figure 4: *Evaluation of upper limit of MIC value from all substrates.*

Substrate 1: Portuguese honey, Manuka honey; Substrate 2: Mexican Yucatan Honey, L-Mesitran soft; Substrate 3: Iranian Honey; Substrate 4: Jujube (Zizyphus Spina-christi) Honey; Substrate 5: Honey and Miconazole; Substrate 6: Monofloral lavender Honey; Substrate 7: Turkish Honey; Substrate 8: Local Produced Honey; Substrate 9: Jarrah Honey, Medihoney, Comvita Honey, Artificial Honey; Substrate 10: Honey, Beeswax and Olive oil mixture.

Discussion

Candida species are prominently known as a primary etiological agents of recurrent and vulvovaginal candidiasis. Fluconazole is one of the most routinely prescribed antifungal agents against candidiasis. Berkow and Lockhart [44] revealed that fluconazole is function by suppressing the cytochrome P450 enzyme 14α-demethylase in the ergosterol biosynthesis pathway which is encoded by ERG11. Numerous *Candida albicans* clinical isolates overexpress ERG11, the gene encoding the target of the azoles. The level of overexpression is low or else noticed in synthesis with other resistance mutations, making it burdensome to evaluate the direct influence of such overexpression on the resistant phenotype. Mutations in Upc2p provide gain of function for the regulator, leading to increased production of Erg11p and constitutive transcriptional activity. This increased production of the azole target dilutes the activity of the fluconazole and results in resistance [44]. Because of fungistatic state of fluconazole, so treatment of *Candida* infections will creates an opportunity to develop acquired resistance. The results of this study showed that fluconazole have positive effect only on *Candida* species and antimicrobial activity while Medical-Grade Honey have the potential positive effect on all attributes in the table 1 such as Non-*albicans Candida* species, *Candida* species, antimicrobial activity, biofilms, antioxidative activity, increased resistance, anti-inflammatory activity, vaginal mucosal response, osmotic activity and pH. Gharibi., *et al*. [45], reported that the frequent used of clotrimazole and fluconazole in the therapy of vulvovaginal candidiasis has shown that the two methods, complaints symptoms of erythema, scratching, itching and edema were reduced among patients. The current study considered the increasing rate of fluconazole resistance drugs among patients with vulvovaginal candidiasis may apparently increases the risk of infection with non-*albicans Candida* species. However, in the United States, Pfaller., *et al*. [46], reported low incidence of fluconazole resistance against *Candida albicans*. Whereas *C. glabrata*, *C. tropicalis* and *C. parapsilosis* have the higher rate of fluconazole resistance. In this study, fluconazole have negative effect on biofilms, non-*albicans Candida* species, pH, an-

tioxidative, vaginal mucosal response, anti-inflammatory, increase resistance and osmotic effect (Table 1). And the findings of this study, is consistent with the study of Riel., *et al* [19]. In the study of Calderon and Clancy [47], revealed that *Candida* species are well known as a normal flora of the human body that have the potential ability to change to pathogenic form that can cause serious infections ranging from superficial infections to life-threatening systemic ailments. Some studies revealed that most of the etiological agents of *Candida* infections are *Candida krusei*, *Candida glabrata*, *Candida parapsilosis*, *Candida albicans* and *Candida tropicalis* which is agreed to the current study (Table 2). The risk factors for candidiasis can be classified into factors that can provide direct pathway, promote colonization and suppress the immune response for Candida infections. Berkow and Lockhart [44], revealed that non-*albicans Candida* species are being isolated more frequently as human pathogens compared to *C. albicans*. The sudden increase rate of non-*albicans Candida* species is apparently due to their inherently high levels of fluconazole resistance. Such mechanisms of fluconazole resistance in emerging *Candida* species include alteration in drug target, increased drug efflux and development of compensatory routes for producing the target sterol. Honey is a natural and secondary product of honey bees collected from blossoms by nectar. Waykar and Alqadhi [48] revealed that honey contains some significant constituents such as organic acid, flavonoids, α-tocopherol, carbohydrates, phytochemical compounds, minerals, vitamins, phenolics enzymes and ascorbic acid. Honey has been reported for its curing effects as antiseptic, antifungal, antibacterial, antiviral agents and commonly used to treat wound ailments globally. Jahdi., *et al*. [2], reported in their randomized, triple blind clinical trial that used of honey vaginal cream and yogurt for seven days amazingly reduced the symptoms of vulvovaginal candidiasis such as secretions, itching and burning when urinating compared to clotrimazole group. Likewise, Fazel., *et al*. [49] revealed that clotrimazole and honey reduced the symptoms of vulvovaginal candidiasis. The consistency may be due to antimicrobial efficacy of honey due to its high osmolality content. Honey is a good preventive agents against eye ailments, sore throat, ulcers, gastrointestinal disorder, cold, burns, fever and cough. Waykar and Alqadhi [48] reported that honey is also used to build up hemoglobin of blood, laxative blood purifier, reducing the risk of cancer, heart disease, immune system decline, inflammatory processes, cataracts, diabetes and indigestion. Hegazi and Abd El-Hady [50], reported that the therapeutical effects of honey products is due to their active antioxidant activity. This study showed that substrate 8 (Local produced honey) have potential antimicrobial activity on *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei*, *Candida kefyr* and *Candida dubliniensis* with the percentage frequency of 20.69% (6.00). Waykar and Alqadhi [48] reported that honey also have the capacity to reduce the risk of conjunctivitis, secretion of gastric acid, protects liver against oxidative damage, improving sperm and serum testosterone ability and impairment of testicular function. The current study shows that substrates 6 (Monofloral lavender honey) had the lowest MIC value with percentage frequency of 4.65% which make it effective to inhibit the growth of all yeasts (Figure 3 and table 2). This study agreed with the reports of Behmanesh., *et al*. [51] that the lavender has numerous antifungal activity against *Candida* species. Contrarily to some reports on the antifungal effects of lavender were inconsistent according to Behmanesh., *et al*. [51]. Behmanesh., *et al*. [51] also reported that antifungal effect of Lavender was significantly positive in some studies but shows very weak inhibitory effect on fungal species. Myriad of years ago, lavender has been used in the treatment of infections in Traditional Chinese Medicine due to its strong antimicrobial activity against bacteria and fungi according to Behmanesh., *et al*. [51]. Essential oil of *Lavandula angustifolia* (Lavender) has some compounds such as linalyl acetate and linalool that potentially inhibit the growth of fungi. Studies revealed that the fungal cell count in tubes with high dilution rate containing lavender essence and lavender infusion was lower compared to clotrimazole tubes. D'Auria., *et al*. [52] reported that that higher dilutions of lavender, decrease its diffusion rate in the tissue and fungal growth. And also elongate the fibers and inhibit the formation of fungus. The infusion of lavender and its essence has a higher antifungal activity against *Candida albicans* compared to clotrimazole. Irish., *et al*. [27], revealed that honey with hydrogen peroxide was found to have a greater antifungal effect compare to others. Irish., *et al*. [27], also reported that honey could also be integrated into a pessary for the treatment of vaginitis. Figure 4 showed the upper limit of MIC value of different substrates. The results revealed that the substrate 5 (Honey and Miconazole) had the highest MIC value with percentage frequency of 14.78% (80.00) and is agreed with the study of Koc., *et al*. [25], reported that all honey samples that were evaluated had antifungal activity as low as 1.25% (v/v) concentration but greatest inhibition was being observed at high concentrations of 40% v/v. And this is consistent with the findings of Al-Waili., *et al*. [28] that the

amount of honey present in the honey mixture of 50% w/v concentration inhibited completely the growth of *Candida albicans*. Concentration of honey ranging from 30 - 50% inhibited the growth of *Candida* species. Koc., *et al*. [25], also reported that multi-floral honey had the highest and phenolic content of antifungal activity. Irish., *et al*. [27] has revealed that honey is finite to topical therapy and might not be used in the treatment of candidemia. The fungal ailments are serious public health challenge. The emergence of fungi resistant to recently available drugs, toxicity concerns and limited spectrum have created an urgent need for effective alternative antifungal agents against systemic and superficial mycoses. The results of this study suggest advance research on randomized controlled clinical trial comparing the efficacy of MGH such as Monofloral Lavender Honey with fluconazole and its practical consideration.

Medical-grade honey (MGH)

The prevalence of high risk of recurrence rate of vulvovaginal candidiasis after fluconazole therapy, apparently, might be attributed to the interaction of fluconazole elements with invasive *candida* developmental stages, hyphae and the yeast [19]. The extracellular matrix inhibits the fluconazole to act on the *Candida* cellular components, and therefore antifungal elements will not have an effect on biofilms [29]. Fluconazole have negative effect on the vaginal mucosal response (Table 1). Myriad of years ago, honey has been used for the treatment and care of ailments due its healing and antimicrobial activities. Acquired antifungal resistance, the epidemiological transpose from *Candida* species to non-*albicans Candida* species, therefore the existence of biofilms require better alternative therapy. Medical-Grade Honey could be an affordable, accessible and effective alternative therapy against vulvovaginal candidiasis [30]. Rigorous guidelines are followed for the establishment of MGH to assure the effectiveness and safety of honey for clinical therapy [31]. More research is needed for the clinical application of honey in order to reduce the formation of biofilm in plastic devices such as urinary catheters [32].

The potency (Antimicrobial activity) of MGH against *Candida* species

MGH has numerous physicochemical properties that shows effectiveness in healing and antimicrobial activities. MGH consists of more than 190 different essential substances such flavonoids, water, glucose, minerals, vitamins, phenolic compounds, fructose, organic acids, enzymes, and other phytochemical compounds [31]. Factors that are responsible for the antifungal potency of honey include sugar-rich composition that attracts the fluid from the surrounding environment, osmotic activity and that will be resulted to dehydration of present microbial pathogens which makes them susceptible [19]. Hydrogen peroxide is one of the most potent antifungal compounds of MGH [20]. The sugars from the honey will come into contact with water in the presence of the enzyme (glucose oxidase) in Medical-Grade Honey then hydrogen peroxide will be formed and released {$C_6H_{12}O_6$ (glucose) + H_2O + O_2 + glucose oxidase → $C_6H_{12}O_7$ (gluconic acid) + H_2O_2 (hydrogen peroxide)} [33]. H_2O_2 (Hydrogen peroxide) is a prominent antimicrobial compound that kills numerous microorganisms that are resistant to antibiotics [20]. The acidic pH component of MGH makes it toxic for most microorganisms to thrive. Other compounds that are present in MGH have a potential antimicrobial potency which include flavonoids, bee defensing - 1, phenolic compounds and methylglyoxal [20]. Apparently, microorganisms are not proficient of developing rapid resistance towards MGH because the antimicrobial activity of MGH is based on various components [20]. MGH usually play a significant role in all *Candida* developmental stages. Fluconazole usually interacts with the first three developmental stages from yeast to invasion by inhibiting with the growth of the *Candida* species, plasma membrane synthesis and adhesion [19]. The biofilm forms a physical defense against the activity of fluconazole by blocking the reaching of the cellular components of *Candida* species [34]. The antimicrobial activity of MGH against biofilms may therefore be a significant and selective component that results in a long-term therapy. The efficacy of honey against *Candida* species has been widely studied *in vitro* (Table 2). In this study, minimal inhibitory concentrations (MIC), content of the findings, efficacy of the honey against *Candida* species were evaluated (Table 2) and effectiveness of fluconazole (Table 1). Further *in vivo* research and evaluation is urgently needed base on the effect of the honey extract.

Effectiveness of MGH against non-*albicans Candida* species

Non-*albicans Candida* species (NAC) initiate a major challenge in the management of vulvovaginal candidiasis. Increase in the resistance of antifungal agents against the disease is directly proportional to the increase of NAC species [35]. Apart of the potent ability of honey against *Candida* species, numerous studies have evaluated the susceptibility of NAC species such as *Candida dubliniensis*, *Candida tropicalis*, *Candida glabrata*, *Candida kefyr* and *Candida parapsilosis* to honey, apparently that can serve the purpose of urgent need for new antifungal agents against the disease [20].

The efficacy of MGH on biofilms

The concomitant increased resistance is usually caused by extracellular matrix of the biofilm, inhibiting antifungal elements from blocking the cellular components of *Candida* species from the host immunity and from penetrating the biofilm. MGH can be the alternative solution for the challenge against the management of *Candida* biofilms. MGH decreases the production of extracellular polysaccharide matrix which stimulates the eradication of mature biofilms and resulted to the blockage of biofilm formation [19].

Impact of MGH on *Lactobacilli*

MGH has no any influence against *Lactobacilli*. However, MGH has some coincidental features on *Lactobacilli* such as maintaining a low pH and the production of hydrogen peroxide. *Lactobacilli* are natural competitors of *Candida* species in the vagina and preserve a healthy vaginal microbiome. Increase in concentration of *Lactobacilli* is inversely proportion to the overgrowth of *Candida* species. *In vitro* studies revealed that MGH does not distort the beneficial effects of *Lactobacilli* [30]. *In vivo* study revealed that honey increased the growth of *Lactobacilli* in rats [36]. Further research is needed urgently to evaluate the effect of honey or honey extract on the total vaginal microbiota in animal model through microbiome assessment.

MGH regulates the vaginal microenvironment

MGH has antioxidative and anti-inflammatory effects that can aid the vaginal environment, especially under inflammation and infections [37]. A pro-inflammatory condition of the vagina makes the tissue susceptible to *Candida* infections [4]. Phytochemical constituents such as vitamin C, flavonoids and polyphenolic agents, are antioxidants present in the MGH, which eventually lessen inflammation and reduce tissue damage and release free oxygen radicals [20]. Apparently, MGH will not fight the infection alone but also will exploit the tissue for new infections by impairing the inflammatory condition and change it towards immunity.

Efficacy of MGH on immunity

Manuka honey generates a spot of death at the surface which kills microorganisms and related native human cells [54]. As the honey migrates deeper into the wound spot, it becomes more dilute. The effect of Manuka honey on neutrophils within inflammatory regions is highly significant to the modulation of tissue template associations and the desired resolution of inflammation and induction of regeneration and healing [54]. The cytokine release results show that of the stimuli examined, lipopolysaccharide is the main driver of the release of the majority of the analytes identified, including both anti-inflammatory and inflammatory signals [54]. When combined with lipopolysaccharide, N-formylmethionine-leucyl-phenylalanine had synergistic effects on release for most analytes [54]. The interferon-γ, lipopolysaccharide group only caused insignificant increase in the release of chemokine ligand-3/macrophage inflammatory protein-1α, chemokine ligand-4/macrophage inflammatory protein-1β, chemokine ligand-20/macrophage inflammatory protein-3α, matrix metalloproteinase-1, and vascular endothelial growth factor at 24 hours associate to lipopolysaccharide alone [54]. The activation of these mechanisms causes release to be increased over the levels observed when only one or two of these mechanisms are activated. The release of Manuka honey into the system caused a change in release that was highly dependent upon the concentration of honey present. 0.5%

honey caused a decrease in all stimulation groups in the release of most analytes. 3% honey caused a decrease in the release of all analytes at all time-points except tumor necrosis factor-α and chemokine ligand-8/interleukin-8. The increase in the release of the cytokines shows a pro-inflammatory effect of the honey related to that results of 3% honey in the study [54]. The mechanisms by which Manuka honey causes the cellular effects are not fully understood, it is predicted that the phenolic components of honey such as known bioactive molecules like pinocembrin and pinobanksin can cross the cellular components [54]. These phenolic molecules neutralize free radicals within the cell and trigger 5' AMP-activated protein kinase phosphorylation which increasing the expression of antioxidant enzymes and modifying various intracellular mechanisms [55]. This mechanism of action is feasible but further research is required to fully validate it and elucidate other possible methods by which honey modifies neutrophil behavior. It was reported that Manuka honey has shown to contain some amounts of lipopolysaccharide [54]. However, these stages are below the minimum required to stimulate most neutrophil inflammatory behaviors [54]. The lipopolysaccharide content may play a significant role in the cytokine context reported in some studies, as one bioactive component among many. The antioxidative and pro-inflammatory activity of MGH also influence the immune response in relation towards changing the microenvironment. Leukocytes move in reaction towards chemokines and cytokines that are produced under the effect of the local microenvironment [38]. By affecting the microenvironment state such as hydrogen peroxide, oxidative, pH and inflammatory state, MGH can influence the immune response and regulate immunological mediators [39]. MGH may trigger the recovery of monocytes and neutrophils to the location of ailment and move the phenotype of macrophages from pro-inflammatory towards anti-inflammatory and producing a defensive microenvironment [40]. The MGH properties such as immunomodulatory may prevent infections by regulating their antimicrobial activity and immune response. Prophylactic activity of an MGH formulation has previously been evaluated in randomized controlled trials, determining a subcutaneous significant in both colic surgeries and equine lacerations [41].

Considerations for MGH utilization

In comparison with fluconazole, MGH strive pleiotropic efficacy and acts through numerous pathways. This may be effective in the treatment of vulvovaginal candidiasis as it can act on appropriate goals. The numerous of antimicrobial system establishes effective killing of the different fungal species irrespective of their resistance state. The MGH mechanisms lead to weakening of the fungal cell membranes, dehydration of the cells, and triggering of intracellular damage, decreasing its reproduction, causing cell death and at the same time inhibiting the risk of resistance.

Principle for selecting the MGH-based conception

Honey exist in different forms with dissimilar antimicrobial activity and composition due to spatiotemporal differences and floral composition. A finite number of MGH-based conceptions that are FDA and CE mark approved exist such as L-Mesitran, Manuka Fill, Medihoney and Activon. Manuka honey contain potent antimicrobial mechanism which is based on methylglyoxal in contrary to hydrogen peroxide (H_2O_2). I selected Monofloral lavender honey including Jarrah, Medihone, Comvita and artificial honey due to their lower MIC values because the substrates with lower MIC values are potent antimicrobial agents against ailments (Figure 3). However, randomized controlled trials and *in vitro* studies against clinical isolates revealed that other types of honey such as L-Mesitran have increased efficacy against mucositis than manuka honey and stronger antimicrobial activity [42,56]. In some studies, the L-Mesitran cream has been used for the treatment of vaginitis and shows potential efficacy on the mycological and clinical cure [19]. The effectiveness of L-Mesitran Soft formulation is due to some supplement such as propylene glycol, vitamins C and E, medical-grade lanolin and 40% MGH. Studies have evaluated the comparison between raw honey component and L-Mesitran Soft against fungi such as *Candida glabrata*, *Candida auris*, *Malassezia pachydermatis*, *Candida parapsilosis*, *Candida albicans* and *Candida krusei* [19]. MGH also showed a synergistic activity with the other supplements of L-Mesitran substrate on the eradication and inhibition of biofilms [43]. L-Mesitran Soft is potent in the treatment of chronic ailments infected with multi-resistant bacteria even when present in biofilms. Studies shows the evidence of the wound healing properties and antimicrobial activity of L-Mesitran Soft with free of any adverse effects [19].

Conclusion

Apparently, the population of women with recurrent and vulvovaginal candidiasis is statistically evaluated to be increased in the next few years. The most routinely used treatment of the disease is fluconazole which is evaluated to become ineffective in the future due to increasing resistance of antifungal drugs. However, MGH might be a promising therapy options in recurrent and vulvovaginal candidiasis. MGH is evaluated to have multiple significant and antimicrobial mechanisms against candidiasis when compared to fluconazole. MGH can eliminate or reduce the effects of antifungal resistant against non-*albicans candida*, biofilms and *Candida* species. Due to antioxidative and anti-inflammatory activity of MGH, the substrate can regulate the microenvironment of vagina from susceptibility of microbial pathogens. MGH has demonstrated a promising and potential alternative treatment against vulvovaginal candidiasis. Further research is needed to examine the potential long-term cure rate and clinical efficacy of Medical-Grade Honey.

Conflict of Interest

The authors declare that they have no competing interests.

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