



Comprehensive Review on *Ficus Deltoidea* Effervescent Mouthwash Formulation in Treating Oral Pathogens

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Article History

Received: 18 May, 2021

Revised: 21 June, 2021

Accepted: 7 July, 2021

Published: 11 July, 2021

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Abstract

Ficus deltoidea or its well-known local name Mas Cotek belongs to the family of *Moraceae*. This native plant is commonly found in Malaysia, other tropical and subtropical countries. Oral periodontal disease is an alarming disease and the utilization of herbal plants in treating oral pathogens has raised attention and concern. Therefore the main objective of this study was to review the effectiveness of effervescent mouthwash formulation of the FDL on treating oral pathogens. Plaque accumulation and oral microorganisms are the main predisposing factors to oral periodontal diseases. Herbal mouthwash has been of particular interest these days to treat oral pathogens. Different effervescent agents such as citric acid, tartaric acid, and sodium bicarbonate were used in formulating effervescent mouthwash by different methods with varying concentrations. FDL leaves have claimed to possess different properties such as antioxidant, anti-diabetic, and anti-inflammatory properties which are helpful in treating many diseases. Post compression parameters such as effervescent time, moisture content, and in vitro antibacterial test were reviewed in this study. FDL has shown a strong correlation to the presence of high content of polyphenols, flavonoids, saponin, tannins, and triterpenoids. In conclusion, the type of preparation chosen is by using wet granulation method and the suitable ratio is 2:1.

Keywords: *Ficus deltoidea* leaves; Effervescent mouthwash formulation; Anti-bacterial; Oral pathogens.

1. Introduction

Oral hygiene is an important aspect in the world. The prevalence of treating oral health is rising in Malaysia. Therefore plenty of products are being marketed in the market to treat oral health as oral health is equally important. Effervescent is defined as the evaluation of bubble of gas from a liquid as the result of a chemical reaction [1]. Advantages of effervescent formulation are convenient, easy-to-use and swallowing of medication is not required. However in the recent years the use effervescent mouthwash have attracted a few due to reasons such as conveniences when travelling and good cleansing agent. Cleansing effect can be seen by identifying the percentage of removal of bacteria from the mouth. The consumption of mouthwash has been increasing in the recent years and patients as well as oral practitioner face multiple barriers as many mouthwash products are coming out in the market with different ingredients and choosing the right mouthwash has become a difficult task. Moreover, brushing and flossing of teeth are the first line treatment choice which is being implemented by oral practitioner.

Periodontal disease is a type of oral pathogens which are known as bacterial infection and some forms are associated with specific organisms [2]. Periodontal disease is defined as a disease which occurs when gums disengage from the teeth as a results of inflammatory response to periodontal disease [3].

According to research, the two key oral pathogen diseases are gingivitis, and periodontitis [4]. Dental caries also occurs in adults and children and is a type of periodontal disease which is rising [5]. Dental caries are unalterable infectious disease of teeth causing cavities to be formed. Gingivitis is defined as inflammation of the gingiva which is reversible. Periodontics is defined as inflammation of the gingival and is distinguish by loss of connective tissue attachment and alveolar bone [4]. These diseases deteriorate the body defends and allow the entrance of opportunistic infections and oral disease is known as a silent killer [5]. Dental caries and periodontal disease leads to an inflammatory condition and infection of bacteria around the gingival epithelial tissue caused by invasion of cariogenic microbes on the tooth exterior through the creation of dental plaques biofilms. *Streptococcus mutans*, *Staphylococcus Aureus*, *Candida Albicans* and *Porphyromonas gingivalis* are among the popular bacteria in the oral cavity [5].

Mas Cotek (FDL) is a native plant and is found widely in Malaysia. The plant is frequently used among the Malay population and is able to be used as a capsule, or tonic tea [6]. FDL have anti-inflammatory, anti-bacterial,

sores, wound healing, rheumatism, antioxidant properties, antidiabetic properties and ulcer healing properties [5]. FDL have shown anti-bacterial effects towards *Helicobacter Pylori* which is the main source of chronic gastritis and gastric ulcer [6]. FDL is also correlated to the presence of high content of polyphenols, flavonoids, saponin, tannins and triterpenoids. Researches have shown that FDL have intimate great antioxidant, anti-bacterial and anti-inflammatory properties. Due to various benefits of FDL, these herbal plant can be considered to treat oral pathogens.

Dental Caries which is also called tooth decay is one of the most widespread chronic diseases worldwide. Dental Caries is formed through a complex interchange over time between acid- producing bacteria, fermentable carbohydrate and the host factors include teeth and saliva [7].

Dental caries is the primary cause of oral pain and tooth decay and can be counted in the early stages. According to research, dental caries is a multifactorial disease that starts with microbiological shift within the complex and is affected by salivary flow and composition, and consumption of dietary sugars. This diseases progresses at a slow phase and can be found in crowns and roots portion of the teeth.

The mechanism of action is the same for all types of caries. Bacteria such as *Streptococcus mutans*, *Staphylococcus Aureus*, *Candida Albicans* which are found in the oral cavity produces weak organic acid as a by-product of metabolism of fermented carbohydrates. This acid causes local pH to fall and results in demineralisation of tooth tissues [7]. Dental caries develops due to demineralisation and remineralisation which can be observed when biofilm pH is restored by saliva and acts as a buffer.

According to a research, periodontal disease is defined as a disease that affects the gingiva and supporting connective tissue and alveolar bone. Periodontal disease are divided into two parts which are those involved with gingivitis and also associated with destruction of underlying structure of periodontium [8]. Also periodontal disease gives rise to heap of germs on the surface of the tooth and under the gingiva. One of the most common type of gingival disease is gingivitis. Gingivitis is distinguish by dental plaque biofilms that leads to soreness of gums. According to research, the sign and symptoms of gingivitis is increased redness, swelling and bleeding of the gingiva when patients brush their teeth [8]. Various factors such as pregnancy, autoimmune system and metabolic disease such as diabetes will increase the risk of occurrence of gingivitis. Downturn within gum inflammation will lead to gum disease. In short, periodontal disease is an interlinkage linking ignition reaction and dental biofilm and smoothen the path for cariogenic bacteria [2]. The bacteria that causes gingivitis is *Porphyromonas Gingivalis*.

1.1. Objectives of Review

The purpose of this review are to:

- Review the different types of effervescent mouthwash formulation and their technique.
- Review the pre and post compression parameters of effervescent mouthwash formulation.

Review the efficiency of FDL extract effervescent mouthwash formulation in contradiction of chlorhexidine gluconate mouthwash.

2. Materials and Methods

2.1. Data Sources and Search

The aim of this study was to review the effervescent mouthwash of the FDL on treating oral pathogens. Electronic search was conducted through Google Scholar, Pub Med and Science Direct. The keywords used were effervescent mouthwash, FDL and Oral Pathogens.

2.2. Studies and Paper Selection Process

The study selected must be in English, able to be access and full text articles. Also, several softwares were used in completing this thesis such as Mendeley and Microsoft Word.

2.3. Leaves Collection

Fresh FDL (Mas Cotek) leaves was purchased from a botany in Malaysia. The collected leaves was then plucked and dried to ensure no moisture was present. The dried leaves was then blended by using a blender until a fine powder was achieved and stored at room temperature.

2.4. Extraction of FDL Extract

The extraction method used was compared between decoction method and lyophilization method. In decoction method, firstly, slogging and weighing was performed on the dried leaves. The leaves were then removed to produce a mixed mixture by steaming at 90 ° C in 1000 mL of purified water for 3 hours. Upon cooling, the mixture was filtered to obtain aqueous extract using a filter paper. The aqueous extract was heated in water and concentrated at 80 ° C. The concentrated aqueous extract was then lyophilised using freeze dryer to produce a powder form. The FDL extract was then transferred and stored in container for succeeding time [9].

2.5. Evaluation of FDL Extract

Assessment of the physical and chemical properties of the FDL extract was carried out to ensure that the formulation remains stable, safe and effective at all times.

2.6. Organoleptic Characteristics

Evaluation of taste, odour, colour and appearance was being conducted on the dried powder of FDL.

2.7. Solubility

Diffusion into purified water or synthetic solvents, for example chloroform and methanol, was performed to check the solubility of FDL [10].

2.8. Swelling Index

In a measuring cylinder, purified water was added and leaves were then added. The volume occupied was measured after undergoing vigorous shaking [10]. Swelling Index is defined as the volume in mL taken up by the swelling of 1 g of herbal material under specified condition. The steps were repeated 3 times and the formula is as follows.

$$\text{Swelling Index} = \frac{\text{Ultimate Capacity} - \text{Starting Capacity}}{\text{Starting Capacity}}$$

2.9. Loss of Drying

A hot air oven was used to heat the FDL extract powder at 90°C and the percentage of moisture loss on drying was calculated using the formula below [10].

$$\text{Loss of drying (\%)} = \frac{\text{Weight of water in Sample} \times 100\%}{\text{Weight of Dry Sample}}$$

2.10. pH

FDL extract was thawed in purified water. The pH of leaves extract was restrained by digital pH indicator [11].

2.11. Percentage Yield

The percentage yield intended by means of the equation beneath [11].

$$\text{Percentage of yield (\%)} = \frac{\text{Amount of leaves extract achieved (g)}}{\text{Amount of leaves sample (g)}} \times 100\%$$

2.12. Bulk Density

The dried leaves extract was weighed and added into a graduated cylinder and the volume was recorded. The powders were then introduced to a tapping in a bulk density apparatus until a constant volume was achieved [12].

2.13. Phytochemical Screening of Extract

The FDL extract are associated with high content of tannins, polyphenol, saponin, flavonoid and triterpenoids.

2.14. Test for Tannins and Polyphenols

The test conducted for tannins and polyphenols was performed by adding a few drops of ferric chloride (III) solution to the leaf extract. The presence of tannins and polyphenols was confirmed when the colour changes to deep blue black [11].

2.15. Test for Saponins

Purified water was added to the FDL extract and the mixture was shaken vigorously. According to research, the presence of saponin was confirmed by performing the foam test whereby if foam is presence, then the saponin was presence [13].

2.16. Test for Flavonoids

The presence of flavonoids was seen through alkaline reagent test. A few drops of sodium hydroxide were added to the leaf extract until an intense yellow colour was formed. Then a few drops of hydrochloric acid was added and was confirmed once it turn to the initial colour [13].

2.17. Test for Triterpenoids

According to research, the presence of triterpenoids was seen when a few drops of acetic anhydride were mixed with the leaves extract and left for boiling and cooling. Then concentrated sulphuric acid was added and a brown ring at the junction of the two layers was observed. Green colour at the upper layer and deep red colour at the lower layer indicated the presence of triterpenoids [13].

2.18. Preliminary Anti-Bacterial Assessment of the Extract

Three types of concentration of the leave extract which were 0.20 mg/mL, 0.30 mg/mL and 0.40 mg/mL was tested for anti-bacterial activity. Then, 100 µL Tetracycline functions as a positive control was added. Mueller

Hinton agar was prepared in the agar plate and let to melt and allowed to be cooled before pouring. The anti-bacterial activity was performed using agar well diffusion method. The strains of bacteria such as *S. aureus*, *B. cereus*, *E. coli*, *Pseudomonas Aeruginosa* were then spread by using sterile cotton bud. A sterilised cork borer was used to grip the agar well. The agar plates were then left in the incubator. Agar well diffusion method was used to determine the anti-bacterial activity and the mean diameter from the three concentration was obtained [14].

2.19. Formulation of FDL Effervescent Mouthwash

FDL effervescent mouthwash was prepared by using the wet granulation method [15]. Firstly citric acid and sodium bicarbonate were milled by using sieve No. 35 and were then blended for 15 minutes. Then 10% w/v of PVP solution which acts as a binder was added and mix thoroughly. After it has already dried, a miller was used in order to pass through the sieve. Then sucrose was added and mixed for approximately five minutes. Lubricant (PEG 6000) was then added.

2.20. Evaluation of FDL Effervescent Mouthwash

Pre and post compression test were performed for evaluation purpose of FDL. In pre compression, test such as angle of repose, bulk density, tapped density, compressibility, Hausner's ratio and moisture content was performed while for post compression test such as tablet shape and dimension, hardness, thickness, weight variation, disintegration time, pH, moisture content and *in-vitro* anti-bacterial activity were evaluated.

2.21. Angle of Repose

The steepest angle of a granulating material is defined as angle of repose. According to research, the formula used for angle of repose is as below:

$$\tan \theta = h/r$$

Whereby θ is the angle of repose while h is the height of the cone and r is the radius of the cone base. Moreover, according to research, if the angle of repose is less than 30° then the material is of free flowing [16].

2.22. Bulk Density and Tapped Density

Bulk density and tapped density has a correlation with the index flow ability [15]. The proportion of the granulated weight to initial volume is known as bulk density while the proportion of the weight of granules to final volume is known as tapped density.

2.23. Compressibility Index

The percentage of compressibility is known as Carr's Index. Carr's Index is 100 times the ratio of the difference between tapped density and bulk density over tapped density [15]. The formula is as below.

$$\text{Compressibility Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

2.24. Hausner's Ratio

The formula used in Hausner's Ratio is tapped density divided by bulk density.

2.25. Moisture Content

Moisture content was performed on granules. The granules was in the desiccator for 6 hours containing silica gel to remove all the moisture left [12]. The formula used was

$$\text{Moisture Content} = \frac{\text{Post-Compression Parameters} \quad \text{Weight of granules before drying} - \text{weight of granules after drying}}{\text{Weight of granules before drying}} \times 100$$

2.26. Tablet Appearance and Proportion

Appearance, size, colour uniformity and surface texture were performed to identify the tablet shape and dimension.

2.27. Hardness

Hardness is defined as the force required to break or crush the tablet. The equipment used was Monsanto hardness tester. Hardness is measured to withstand the mechanical shocks of handing, manufacturing, packaging and shipping of a tablet. Also according to research, hardness affects disintegration. If the tablet is too hard then it may not disintegrate in the required period of time [17]. Ten tablets was taken and the mean hardness of the tablets was taken. The limit must be within 5 kg to 8 kg.

2.28. Thickness

According to research, tablet thickness depends on the force of compression. The thickness was investigated by measuring the thickness of twenty randomly taken tablets and the average thickness was calculated. A deviation of 5% is allowed [15].

2.29. Weight Variation

Weight variation was done to ensure there is no uneven feeding which will lead to uneven weight. Thirty tablets were weighed and each weight was measured. Then the average weight was also calculated and then the percentage deviation range was seen [16].

2.30. Disintegration Time

Disintegration time was performed on tablets. One tablet was put at a temperature of 30 ° C in 150 mL beaker which contains 100 mL of purified water. Time taken to disintegrate into the water was noted and the steps were recurrent for another five pills and the mean was noted [15].

2.31. pH

Five tablets were added into five different beakers. A pH meter was used and the average pH was recorded [15].

2.32. Moisture Content

The tablets and granules were stored in the desiccator for 6 hours containing silica gel to remove all the moisture left [12]. The formula used was.

$$\text{Moisture Content} = \frac{\text{Mass of granules prior to drying} - \text{Mass of granules following drying}}{\text{Mass of granules prior to drying}} \times 100$$

2.33. *In vitro* Anti-Bacterial Activity

The ready FDL effervescent mouthwash formulation was transferred to 20 mL of water and tested by agar well diffusion method for anti-bacterial activity. Mueller Hinton agar was first used cooled and refrigerated to 45°C. It was then poured onto sterile agar plates. The strains of bacteria such as *S. aureus*, *B. cereus*, *E. coli*, *Pseudomonas Aeruginosa* are then spread by using sterile cotton bud. A sterilised cork borer was used to punch well on the agar. Then 100 µL of each FDL effervescent mouthwash formulation samples and control was introduced into the well. The agar plates were then left for incubation at 37°C for 24 hours. The anti-bacterial activity was determined by using the agar well diffusion method technique and disk diffusion method [18].

3. Results and Discussion

FDL (Mas Cotek) belongs to the family of *Moracea* [19]. This native plant is found widely in Malaysia, other tropical and subtropical countries. The uses of these leaves are common for women who just gave birth, to retrieve energy, replenish blood flow and for beauty purpose [20].

Figure-1.1. Leaves of FDL plant



Table-1. Structures of isolated compounds from FDL

Name	Structure
Catechin	
Vitexin	
Naringin	
Ellagic acid	
Gallic acid	
Ferulic acid	

3.1. Effervescent Agent Profile

The effervescent agents selected to be used in this study are citric acid, sodium bicarbonate and mannitol.

3.2. Citric Acid

Citric acid is a weak organic acid and occurs naturally in fruits such as oranges, lemons and limes.

Table-1.1. Physicochemical properties of citric acid

Physicochemical Properties	Characteristics
IUPAC name	2-hydroxpropane-1,2,3-tricarboxylic acid
Molecular formula	C ₆ H ₈ O ₇
Chemical structure	
Appearance	White or Colourless, crystalline solid
Odour & taste	Odourless and acid taste

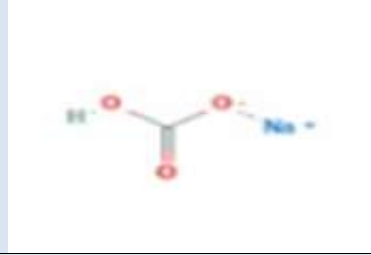
Acidity or alkalinity	pKa = 2.79
Density	1.665 g/cm ³ at 20°C
Solubility	Very soluble in water; freely soluble in ethanol, soluble in ether
Melting point	153°C
Action and use	Excipient
Storage	Store in air-tight containers to avoid moisture. Keep away from strong oxidants, strong bases, metal nitrates and metals.

Source: PubChem Compound Database, 2019

3.3. Sodium Bicarbonate

Sodium Bicarbonate is the monosodium salt of carbonic acid. The main function of sodium bicarbonate is as an element in neutralization with citric acid to process carbon dioxide as effervescent agent.

Table-1.2. Physicochemical properties of sodium bicarbonate

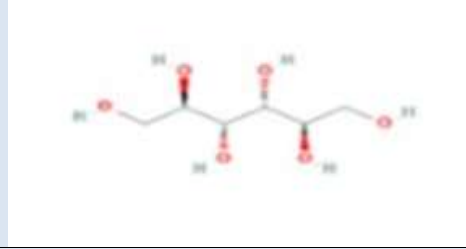
Physicochemical Properties	Characteristics
IUPAC name	Baking soda
Molecular formula	NaHCO ₂
Chemical structure	
Appearance	White crystalline powder or lumps
Odour & taste	Odourless and slightly bitter taste
Acidity or alkalinity	8.0-8.6 in 1% w/v solution
Density	2.1 g/cm ³ at 20°C
Solubility	Soluble in water; Insoluble in ethanol
Melting point	50°C
Action and use	Excipient
Storage	Store in air-tight containers to avoid moisture. Keep away from acid.

Source: PubChem Compound Database, 2019

3.4. Mannitol

Mannitol is a type of sugar alcohol which functions as a sweetener. Mannitol is poorly absorbed from the intestine.

Table-1.3. Physicochemical properties of mannitol

Physicochemical Properties	Characteristics
IUPAC name	(2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol
Molecular formula	C ₆ H ₁₄ O ₆
Chemical structure	
Appearance	White crystalline powder or free flowing granules
Odour & taste	Odourless and sweet taste
Acidity or alkalinity	8.0-8.6 in 1% w/v solution
Density	1.52 g/cm ³ at 20°C
Solubility	Soluble in water
Melting point	166-168°C
Action and use	Excipient
Storage	Store in room temperature and protect from freezing

Source: PubChem Compound Database 2019

3.5. Evaluation of FDL Leaves Extract

FDL leaves extract were evaluated by various physicochemical properties such as percentage yield, solubility, and pH. According to Zakaria, Z.A., *et.al* FDL leaves powder extract was extracted by two different methods such as decoction method and lyophilisation method [21]. The lyophilisation, powdered FDL leaves was heated in distilled water at 60 °C for 2 days while in decoction method powdered FDL leaves was boiled twice and heated at 60°C in 1L distilled water for 4 hours. Salleh and Ahmad [9]. Lyophilisation method showed higher percentage yield (17.8%) compared to decoction method (7.36%) due to temperature and time taken. Studies have shown that as the time taken increases, the percentage yield also increases and as the temperature increases, the percentage yield also increases [22].

Solubility and pH also plays a significant contribution in FDL powder extract. Vilash, *et.al* cited that solubility studies were conducted by distilled water, alcohol soluble (methanol) and petroleum ether soluble (chloroform). Results have proven that petroleum ether (chloroform) was insoluble in water followed by methanol and lastly distilled water because the bonds of interaction of distilled water were very strong. According to Sule W.F, *et.al*. pH can be affected mainly by the proportion of effervescent agents such as citric acid and sodium bicarbonate. According to Zakaria, Z.A, *et.al* as the concentration of citric acid increases, the pH of the solution decreases. pH assists in shortening the rate of release. Once the effervescent time is shorten then the percentage yield will be greater. Viscosity of the extract has a strong correlation the pH of the solution because viscosity can affect the absorption rate of the extract and thus lowering the pH of the solution.

3.6. Effervescent Mouthwash Formulation

The different techniques used to formulate effervescent mouthwash were wet granulation dry granulation, and direct compression method. According to Aslani & Eatesam, wet granulation method showed good ability to improve the flow property of powders compared to other method [23]. The flow property of the powders were determined by pre- formulation test which were angle of repose, Hausner's ratio and compressibility index. Other factors such as particle size also has a close relationship with flow property of powder. This study confirmed that an increased in particle size will increase the flow property of powder were as partical size decreased the flow property of powder will also decrease.

Palanisamy *et.al* formulate aclonefac effervescent tablets by direct compression and wet granulation method with varying concentration of citric acid and sodium bicarbonate. The major issues in direct compression method were capping and sticking, whereas in wet granulation method the capping and sticking problem were less, due to the environmental moisture were protected by the acid and bases. Palanisamy, *et al*. [24]. Capping and sticking problem were minimized by adding 0.5% of lubricant in formulation of effervescent tablets [25].

According to Agrawal, Rajesh and Yadav Naveen, wet granulation method showed more comprehensive results compared to dry granulation and direct compression method. This is because the presence of binder solution in wet granulation method allows better distribution of colour, increase the solubility of the drugs, prevents segregation of powders and makes hydrophobic surfaces more hydrophilic. Due to high shear mixture rate in wet granulation allowed the tablets to distribute uniformly. Addition of binder in wet granulation method allowed the tablets to hold molecules together to create surface tension on water [26].

3.7. Medicinal Properties of FDL

3.7.1. Anti –Diabetic Effect

Various researches have formulated herbal extracts as an alternative treatment to treat diabetes mellitus. According to Misbah *et.al*, polar component of *Ficus Deltoidea* plant showed anti-diabetic properties such as reduction in hyperglycaemia which is characterised by rise in blood sugar reading [27]. Adam, Zainah, *et.al*, cited that *Ficus Deltoidea* has proven result to reduce hyperglycaemia at different pyramidal states. Two different methods were used for extraction such as hot and cold aqueous extraction was carried out. Cold aqueous extract showed significant benefit of glucose uptake under insulin stimulated state while hot aqueous extract showed insulin secretory action through K⁺ channel dependent pathway [28].

According to Bunawan, *et.al* FDL showed visible α -glucosidase and α -amylase inhibitory effects to control postprandial hyperglycemia [6]. Postprandial hyperglycemia mechanism was mediated through enhancement of glucose uptake into muscle cells. Three different extraction method such as hot aqueous, ethanolic, and methanolic extraction method was performed on α -glucosidase activity. Methanolic extraction method was found to be the most potent inhibitor for α -glucosidase. Pure bioactive constituents, partitioned extracts were the subject of α -glucosidase assay. The highest dose of 2 g/kg were administrated and both vitexin and isovitexin significantly reduced postprandial blood glucose level in mice. The fruits of FDL were separately extracted and antidiabetic activities were evaluated according to the ability of the extract to inhibit both yeast and mammalian α -glucosidase and α -amylase. Depending on the dose administered the level of hindrance are evaluated. A dose of 1000 mg/kg was able to hinder α -glucosidase and α -amylase activity.

Diabetes mellitus was able to disrupt the normal function of blood clotting mechanism in an individual's body. Studies have shown that *Ficus Deltoidea* was able to normalise the blood clotting mechanism. According to Nurdiana, S. *et.al* the study was conducted on two groups of diabetic rats. The extract of the FDL leaves were orally administered to one group of rats while the other was injected with ethanoic extract. The presence of an injection showed significant result in blood clotting rate as well as a sharp decrease in blood sugar reading. This study has shown that systemic route of administration does not affect first pass metabolism and rapid action was achieved [29].

3.7.2. Anti-Inflammatory and Anti-Oxidant Effect

Inflammation is defined as the body's response to cellular injury and they are categorised into two types such as acute and chronic inflammation. Acute, chronic inflammatory responses and pain-associated inflammatory responses are easily treated as FDL possess anti-inflammatory activity on enzymes in the body such as lipoxygenase, and hyaluronidase.

Anti-inflammatory activity was evaluated using formalin test. Formalin test was conducted to attenuate inflammatory mediated pain. 0.9% of normal saline and 100 mg/kg of acetylsalicylic acid was injected to five group of rats intraperitoneally. Acetylsalicylic acid was used as positive control due to the ability of this drug to treat analgesic, anti-inflammatory and as an antipyretic agent around the world. The pain induced from formalin test was due to peripheral tissue inflammation and a variety of chemical mediators that alter the function of peripheral afferent [21].

Three different *in vitro* assays were used to determine anti-inflammatory activity of FDL extract such as lipoxygenase, hyaluronidase and TPA-induced oedema. All the three assays showed anti-inflammatory activity with TPA-induced oedema recording the highest reading [30]. Lipoxygenase activity was measured using spectrophotometric method. Test samples and reference standard were dissolved in methanol and sodium phosphate buffer solution was added. The hyaluronidase assay was conducted by calculating the percentage ratio of the absorbance in the presence of test compound versus absorbance in the absence of enzyme. Acetone was used as a control for TPA-induced oedema and was applied to the inner surface of the right ear of each mouse before TPA was applied.

According to Misbah *et.al*, the phenolic content correlated well with antioxidant activity of the crude extract of the leaves but not the fractions [27]. In addition, free radicals are unstable compounds which affects the normal metabolic functions in the body. In this study conducted by Ramamurthy, Srinivasan, *et.al* antioxidant effects of *Ficus Deltoidea* was determined using three different extract which is methanol extract, hexane extract and chloroform extract and two different methods such as ferric thiocyanate (FTC) and thiobarbituric acid (TBA) method. It was concluded that hexane extract recorded the highest antioxidant effect (259.2 mg/g) followed by methanol (245.2 mg/g) and lastly chloroform extract (159.2 mg/g) and the fruit of FDL has exhibit good source of antioxidant [31].

Lastly, according to Soib, Husnul Hanani, *et.al* the antioxidant activity was performed by determining the total phenolic contents (TPC) method. In this study, a Folin Ciocalteu reagent was added into three samples and one standard. Na₂CO₃ was added and left for one hour. The third sample was rich with phenolic content followed by the second extract and then the first extract. The metabolomic of plants could be one of the cause of the activity tested [20].

FDL extracts have shown great phytochemical screening such as tannins, phenols, alkaloids, saponin and flavonoid. Phytochemical screening of FDL extract contributes to anti-bacterial activity. The presence of tannins and phenols were confirmed by ferric chloride (III) test. The solution will turn blue-black upon addition of ferric chloride (III) solution. The presence of saponin were confirmed by the presence of foam when shaken vigorously. Ramamurthy, Srinivasan *et.al*, cited that the presence of flavonoids, were confirmed by performing alkaline acid test. FDL extract showed intense yellow colour upon addition of sodium hydroxide and turned colourless again after addition of hydrochloric acid [31].

3.7.3. Effervescent Time

Effervescent time is defined as the time taken for a tablet to dissolve when placed in water. Various factors such as presence of binders and lubricants, tablet size, temperature, humidity and type of hopper feed causes variation in effervescent time [32]. Effervescent time is mainly distinguish through formulation of tablets and granules. According to, Tekade, Bharat W., *et.al*, ten formulation of diclofenac effervescent tablets were formulated by varying the concentration of effervescent agents such as citric acid, sodium bicarbonate, PVP and PEG 6000. In this study, PVP was used as a binding agent while PEG 6000 was used as a lubricant. The disintegration time for all ten formulation was between 3-9 seconds. Among the ten formulation F10 shows good effervescent time (3 seconds) because the amount of binder and lubricant used was in less concentration [33].

According to Patel, Jitul B., *et.al* ten different formulation of ibuprofen effervescent tablets were formulated by varying the concentration of effervescent agents such as citric acid, sodium bicarbonate cross-povidone and PVP. The effervescent time recorded for all ten formulation were between 120-310 seconds. In this study, cross-povidone was used as superdisintegrants for F9 and F10 while a small percentage (2%) of PVP was used as binding agent for F7-F10. Superdisintegrants helps tablets to swell and generates hydrostatic pressures necessary for rapid disintegration in the mouth. Although various superdisintegrants are able to speed up the rate of release of a drug, cross-povidone swells very little and returns to original size after compression thus superdisintegrants was not effective in speeding up the rate of release [34].

Aslani & Fattahi formulated potassium citrate effervescent tablets by using different concentration of binding agent such as PVP and HPMC (4%) with varying concentration of effervescent agent. The disintegration time for all six formulation were within 3 seconds [15]. Studies show that PVP was more effective than HPMC due to lower work of cohesion and adhesion of HPMC. Faster dissolution of API by PVP rather than HPMC makes PVP the better choice as a binding agent. Among six different ratio 2: 1 showed the most effective effervescent time due to various reason such as better solubility, and low pH value [35].

According to Mizumoto, Takao, *et.al* cited that effective effervescent time was significant because it measures how quickly a tablet can react in the presence of water to achieve optimum concentration. Furthermore, hardness plays a significant role in effervescent time. There was a correlation between disintegration rate and compressibility in order to ensure adequate hardness of the tablet is achieved and to maintain integrity under shock and abrasion [36]. Bhattacharyya, Sayani, *et.al* cited that effervescent time was conducted on granules by wet granulation method and varying the concentration of effervescent agent such as tartaric acid, sodium bicarbonate. The effervescent time recorded was very much less (20 seconds) than the normal 3 minutes. This is because tartaric acid had very low solubility. Effervescent time is closely correlated to moisture content. As the moisture content decreases, the effervescent time decreases because the absorption rate will be less [37].

3.7.4. Moisture Content

According to Gautam, Archana, *et.al*, the moisture content for effervescent tablets were evaluated by using moisture balance. The moisture content achieved was less than 0.25%. One of the factors could be due to drying time. Increased the drying time reduced the moisture content. Another factor that could affect the moisture content was temperature. Temperature must be suitable for proliferation of living organisms and to ensure activation of enzymes does not occur [38].

According to Vemula, *et.al* moisture content test was conducted on ten different formulation of fast – disintegration tablet of flurbiprofen by using moisture balance. The wetting time recorded was between 30 seconds to 45 seconds. This is because, the moisture content was said to be closely related to the inner structure of the tablet and mimics the action of saliva in contact with the tablet. According to Vemula, *et.al* the moisture content for all ten formulation was rapid due to ability of the tablets to swell and the capacity of water absorption [16].

PS, Mohanachandran *et.al* conducted a research on twelve different formulation and evaluation of mouth dispersible tablets of amlodipine besylate. The method used was direct compression method and by using a petri dish. Various superdisintegrants such as Sodium Starch Glycolate, Cross-Povidone and Croscarmellose sodium for the first nine formulation while for the final three formulation, combination of superdisintegrants were used. The wetting time was rapid for all the twelve formulation ranging between 55-67 minutes. However the wetting time for formulation using croscarmellose (F6) was less due to low solubility of croscarmellose. Combination of superdisintegrant showed very less wetting time (55 minutes) [39].

According to Bhattacharyya, Sayani, *et.al* titration method was used to determine the water content. In this study, the moisture content was found to be in the range of 0.01-0.06%. Low moisture content indicates the ability of the granules to retain effervescent quality and free flow ability. Crospovidone which acts as a superdisintegrants have shown more moisture content than the other formulation while formulation containing mannitol showed the least moisture content because mannitol acts as sweetening agent and does not affect the moisture content [37].

3.7.5. In Vitro Anti- Bacterial Test

According to Samah, Othman, *et.al*, *in vitro* anti –bacterial study on aqueous extract of *Ficus Deltoidea* was performed by varying the concentration at 10 mg/mL, 20 mg/mL and 50 mg/mL respectively by disc diffusion method against a few gram positive as well as gram negative bacteria. Gram positive bacteria that was used were *Staphylococcus aureus* and *Bacillus subtilis* while gram negative bacteria were *Escherichia Coli*, *Pseudomonas aeruginosa*, and *Candida Albicans*. Anti-bacterial study was determined by measuring the inhibition zone and minimum inhibitory concentration. Bacteria growth was observed on Gram positive bacteria such as *S aureus* with an inhibition zone of 15.67 mm. Minimum inhibitory concentration is known as the lowest concentration of antimicrobial agent to prevent the growth of bacteria. The lowest minimum inhibitory concentration measurement recorded was *S.aureus* (3.125 mg/mL) while *B.subtilis* recorded the highest minimum inhibitory concentration (25 mg/mL) [40].

According to Jamal, Parveen, *et.al in vitro* anti- bacterial study on FDL extract was performed by disc diffusion method and agar well diffusion method. The bacteria used were gram negative (*E.coli*) and gram positive (*B.Subtilis*). In disc diffusion method, DMSO was used as a control. About 10 mg/mL of gram negative bacteria (*E.coli*) and was placed in the Mueller Hinton agar plates and the zone of inhibition was recorded by three different extraction method such as ethanol, methanol and distilled water extract. *E.coli* showed a clear area around the well with no bacterial growth for all three extract. Ethanol extract recorded the highest zone of inhibition for *B.subtilis* (12.0 mm) while distilled water extract recorded the lowest zone of inhibition for *B.subtilis* (8.0 mm) [41]. In the agar well diffusion method, 20% of stock solution was prepared in pure DMSO and 0.1% inoculum was spread uniformly over the surface of the Mueller Hilton agar plate. The zone of inhibition for agar well diffusion method was recorded the lowest (6 mm) for gram positive bacteria (*B.subtilis*).

According to another research, the anti-bacterial test of FDL extract was conducted at different concentration 20 mg/mL, 40 mg/mL, and 60 mg/mL by using disk diffusion method. The bacteria used were gram negative bacteria (*E.coli*) and gram positive bacteria (*S.aureus*). Minimum inhibitory concentration (MIC) was determined by a two - fold broth micro dilution method and *E.coli* showed higher MIC reading (150 microgram/mL) against *S.aureus* (130 microgram/mL) [42].

According to Wei, Lee Seong, *et.al* anti-microbial activity was performed against *Helicobacter pylori*. The bacteria was isolated and streaking test was performed to identify any bacterial growth is present. The minimum inhibitory concentration level was recorded. However there were no proper studies on the MIC value against *Helicobacter Pylori* because this bacteria showed better performance in anti-inflammatory effects of FDL. Other microorganisms such as *E.coli*, *Klebsiella sp* *Pseudomonas aeruginosa* and *Streptococcus mutans* was also tested.

The minimum inhibitory concentration was recorded and ranged between 31.26 mg/L to 125 mg/L *Streptococcus mutans* bacteria showed the least minimum inhibitory concentration of 31.25 mg/L [43].

4. Conclusion

In a nutshell, the scientific research review provides a new insight into effervescent mouthwash formulation using a native plant in Malaysia known as *Ficus Deltoidea*. The plant has received increasing attentiveness in recent years. *Ficus deltoidea* has been reported to have favourable pharmaceutical utilization as an anti-diabetic, anti-inflammatory, anti-nociceptive, antimelanogenic, antiphotaging, antioxidant, antiulcerogenic, and antibacterial agent. FDL extract has been recommended to treat oral pathogens and reported as diverse therapeutic potential without any significant toxic effect. Hardly any reviews have been revealed on *in vitro* outcome on FDL extract in opposition to oral pathogens and a substantial command in dentistry for an up to date medium to vanquish microbes, revamp the standard of dental therapy and ease dental procedures. These may assist to nourish greater comprehension of this highly exception plant for lucrative utilization on herbal mouthwash formulation.

Acknowledgements

First of all, I would like to express my deepest gratitude to my supervisor, Dr. Senthil Adimoolam for his patience, encouragement and inspiration in lending a helping hand to me to conduct this review and complete my dissertation writing. He was always present whenever needed and I am utterly grateful to be one of his research student. He also gave me plenty of guidance even after changing the topic to a comprehensive review and made sure to clarify all my doubts.

Next my sincere gratitude to both my parents Mr Bhashkar Prabhudas and Mrs Tarla Ramniklal alongside my siblings Mr Rahul Chitalia and Ms Kinjal Khandhar and my family members for always being there by my side and providing me encouragement and support throughout this research project.

I would like to express my deepest appreciation to both my two friends Boey Hong Jun and Lee Ee Cheng for always assisting and guiding me whenever possible in completing this review.

I would like to express my deepest appreciation to Dr. V. Appalaraju for his contribution for me to complete this dissertation. Moreover, I am grateful to our dean, Prof. Dr Munavvar Zubaid Bin Abdul Sattar for providing this opportunity to participate in this research.

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