REVIEW ARTICLE

Potential Effect of Nutritional Fruits on Gout Therapy - A Review.

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Abstract

Gout is a disease caused by the deposition of monosodium urate crystal (MSU) in the tissues. The rise of uric acid over a specific threshold indicates uric acid crystal formation in gout. Pharmacological and non-pharmacological treatments have been widely developed and used to treat gout. Therefore, in this review, we discuss the current update of the potential effect of several nutritional fruits (cherry, apple, pineapple and sugar apple, respectively) on gout therapy. Thus, this review aims to outline the potential of these nutritional fruits in treating gout via *in vitro, in vivo* and clinical trials. A depth search was done on databases like PubMed, Google Scholar, Scopus and Web of Science to identify potentially relevant articles. The finding reveals that these fruits halt the production of the formation of uric acids due to the presence of several phytochemical constituents such as flavonoids and phenols (quercetins, catechin, epicatechin, anthocyanin, malic acids, sinapinic acids and etc), proteins, and vitamins (A, B and C). Moreover, these fruits also contain anti-inflammatory (anthocyanins, chlorogenic acid, pomolic acid, maslinic acid, bromelain, caryophyllene oxide, cyclosquamosin D and flavonoids, respectively) and antioxidant agents (polyphenols, quercetin, catechin, epicatechin, sinapinic acids, flavonoids, phenols and flavones, respectively) that are beneficial for the inflammation in gout that have been demonstrated via *in vitro, in vivo,* and clinical studies which were highlighted in this review. Collectively, these four potential fruits have been shown to reduce uric acids as well as inflammation, however, cherry is the one showing the highest potential in promoting healing of gout and can be developed as a promising future gout therapy.

Keywords: *Gout, Cherry, Apple, Pineapple, Sugar apple.*

Introduction

Gout is a disorder due to deposition of monosodium urate crystal (MSU) in the bone, soft tissues and joints [1]. Sign and symptom of gout arised from hyperuricaemia which is a condition of high serum uric acid (SUA) levels above 7.7 mg/dl in men and above 6.6 mg/dl in women [2]. Common clinical presentation of gout are gout flare, arthritis, or tophi [1]. Several risk factors for gout include sex, genetic variations, obesity, insulin resistance, medications, and patient with kidney disease due to reduced renal clearance of urate[3]. Recent figures of the prevalence and incidence of gout range from 1% to 6.8% and 0.58 to 2.89 per 1,000 person-years, respectively. With advancing age and among certain ethnic groups, gout is more common in men than in women[4]. Gout prevalence data in developing nations is limited, although general gout prevalence in these countries is lower than in more developed countries. According to the Community Oriented Program for Control of Rheumatic Diseases (COPCORD), the prevalence of gout in Asian countries, Indonesia, recorded the highest prevalence of gout among the adult population (1.7%), followed by Kuwait (0.8%). The remaining Asian countries, including Bangladesh, China, India, Iran, Malaysia, Pakistan, Philippines, Thailand, and Vietnam, were classified as countries with low gout prevalence (<0.5%) [5][6]. Until recently, no specific data was published by the National Health and Morbidity Study (NHMS) regarding the incidence and prevalence of gout.

A new clinical staging system for gout and hyperuricaemia was designed based on the key aspects of the pathological basis of the disease, which include Stage A: hyperuricaemia, but without evidence of MSU crystal deposition or symptoms of gout, Stage B: MSU crystal deposition by microscopy or advanced imaging, but without signs or symptoms of gout, Stage C: MSU crystal deposition with prior or current symptoms of acute gout flares, and Stage D: advanced gout requiring specialist interventions[7]. When immune cells engage with monosodium urate crystals, a gout flare occurs, resulting in an acute inflammatory episode. Immune cells generate the cytokine interleukin (IL)— 1β that plays a key role in gout flare-up inflammation [8].

Although many drugs have been developed and proposed to improve healing of gout, the used of fruits containing anti-hyperuricaemia and anti-inflammatory agent could be benefits in treating gout. Several studies have demonstrated that fruits like cherry, apple, pineapple, and sugar apple have a potential in reducing the level of uric acids and able to treat the inflammatory in gout [9,26-27,47-48,59-62]. It has been reported these fruits contain phytochemical constituent like alkaloid, phenolic, tannin, and flavonoid[10-11]. This review summarises the potential of fruits that can be used to treat gout. Future prospect for the development of gout treatments utilising these potential fruits are also being highlighted. To date, treating gout using fruits have been reported by several researchers. Therefore, the focus of this review was on the *in vitro*, *in vivo*, and clinical studies related to the used of fruits in treating gout.

Current treatment of gout

In a gout flare, therapy aims to alleviate pain and impairment quickly and safely. The gout flare normally subsides completely without treatment within a few days to several weeks, especially in early illness. Most guidelines available from different regions recommended rest and prompt treatment with full doses of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids as the first-line treatments to treat gout flares [12]. The considerations of selecting the treatment choices for gout flare are varied across the guidelines depending on their preferences, patient's contraindications toward corticosteroids, availability of the second line and third line medications, duration of the onset of the flare, and strength of the dose. For patients with contraindications to both NSAIDs and/or colchicine or were ineffective, canakinumab, an

anti-interleukin-1β monoclonal antibody, may be an alternative for such patients[13]. The study of two 12-week randomised, multicentre, active-controlled, double-blind, parallel-group core studies significantly showed that during an acute flare, a single dose of canakinumab gives immediate and effective pain relief, as well as a reduction in symptoms, signs, and inflammatory markers, and even a significant delay in the time to the first new flare and a lowered risk of a new flare [13].

In treating persistent gout, the long-term use of urate-lowering therapy (ULT) is recommended by the American College of Rheumatology (ACR) [14]. Other available guidelines from different regions are in consensus in accepting this. As for the indication, starting ULT should clearly be justified with certain clinical manifestations, such as frequency of acute flares, presented with tophi, renal stones, gouty arthropathy, radiographic changes of gout, and comorbidities such as chronic kidney disease (CKD) [12&15]. The primary and most prescribed first line ULT is allopurinol (AP). Another xanthine oxidase (XO) inhibitor, febuxostat, a uricosuric drug (probenecid, benzbromarone) and pegloticase, a recombinant pegylated uricase administered intravenously, are among the second line therapies [16][18]. A treat-to-target SUA of less than 6 mg/dL (360 µmol/L) and often below 5 mg/dL (300 µmol/L) in those with features of severe gout, such as tophi, are recommended by the ACR guidelines[17] and European League Against Rheumatism (EULAR) [15] to permanently resolve the underlying trigger for acute flares and joint destruction.

Other drug option is selective uric acid transporter 1 (URAT1) inhibitor (lesinurad) [18]. However, these approved drugs to treat acute and chronic gout have adverse drug effects such as renal dysfunction, overproduction of stomach acid, Cushing's syndrome, metabolism disorder, hypertension and hypotension, and irritation of the gastrointestinal tract [18]. The urate-lowering medications now recognised by the FDA include allopurinol, febuxostat, probenecid, and pegylated uricase (pegloticase). Probenecid is only sometimes used since it raises the risk of urolithiasis, has known drug-drug interactions, and works best in patients with GFRs of 950 mL/min or above [19]. NSAIDs, colchicine, and glucocorticoids are conventional medications used prophylactically while initiating ULT and treating acute gout episodes. Unfortunately, these drugs have a potential for both GI and renal damage, hyperglycaemia hypertension, dyslipidaemia, fluid retention, psychosis and agitation which may make them inappropriate for a certain patient population [20].

Fruits and their potential in treating gout

Cherry

Cherries are generally divided into two types: which are sweet (*Prunus avium* L.) and sour or tart (*Prunus cerasus* L.). *Prunus avium* L. (sweet cherry) is geographically distributed all over the world and has a high prevalence in temperate regions including most of Europe (Mediterranean and Central), North Africa, Near and Far East, South Australia and New Zealand as well as temperate regions of the American continent (USA, Canada, Argentina and Chile) [21 - 22]. Bing is the most common variety of sweet cherry grown in the US and it produces large, firm black fruits while Montmorency cherry is the most common grown tart cherry (*P. cerasus*)[22]. Despite its small size, cherry is considered a nutrient-rich fruit and in recent years, it has attracted attention and is deemed to be one of the non-pharmacotherapeutic option for variety of illnesses. Cherries are high in vitamins A, C, and E as well as phenolic such anthocyanins [22]. People enjoy cherries in a variety of ways. Russians often drink coffee with a little of cherry jam added to it, while Hungarians use cherry to prepare cold soup during summer seasons. Other than that, Germans distill cherries into a prized brandy known as Kirschwasser [23].

Although the USA has historically been the world's largest cherry exporter, Turkey currently holds the title as the world's largest cherry producer, followed by the USA and Iran. The production of tart cherries is increasing every year worldwide from 1.14 to 1.38 million tons between 2006 and 2016. The largest tart cherry harvesting area in the world is Europe (66%), which accounts for 62% of total world production [24]. These days there is an increasing demand of the production of dietary supplements with cherries as it is believed and proven in previous studies to relieve joint pain, act as a prophylaxis of gout, improve sleep regulation, promote healing following strenuous activities and more. In addition to raw cherries, there are many cherry products on the market such as juices, powders, concentrates and extracts. An 8-ounce bottle of blended tart cherry juice is equal to 50 cherries [25].

Urate crystal-induced inflammatory reaction stimulate the production of tumour necrosis factor (TNF)-α, IL-6 and chemotactic IL-8. Cherry extract can reduce levels of certain cytokines such as IL-1β, TNFα, IL-6 and IL-17 in affected joints. It was also reported that the anthocyanins in cherry extract strongly inhibit key enzymes involved in inflammation such as cyclooxygenase 1 and 2 (COX-I and COX-II) [26][27]. Eating cherries has also been reported in previous studies to be effective in reducing uric acid levels. Anthocyanins, a phenolic compounds that belong to the flavonoid family, are water-soluble pigments with antioxidant and anti-inflammatory properties [28]. Cyanidin, pelargonidin, peonidin, delphinidin, petunidin, and malvidin are the main anthocyanins in cherries in which cyanidin is among the most common compound [29].

Cherries are known as fruits with high antioxidant properties. The metabolic process in normal cells produces toxic reactive oxygen species (ROS) and nitrogen species that lead to oxidative stress resulting in severe cell dysfunction, direct cell damage and even death of cells [30]. Oxidative stress may contribute to the expression of gout which is triggered by the generation of ROS and pro-inflammatory cytokines [31]. The enzyme xanthine oxidoreductase, which is responsible for the conversion of hypoxanthine into xanthine to urate in the final process of purine metabolism, is also accountable for the formation of ROS [32]. It is known that anthocyanins and other phenolic compounds in cherries also possess antioxidant properties [28 – 29]. As free radical scavengers, phenolic antioxidants disrupt the oxidation process and ultimately reduce volatile decomposition products formation [33]. It is believed that oxidative stress can trigger an inflammatory biochemical cascade in the body, which can lead to gout and other degenerative diseases over time.

The concentrate of tart cherry juice has the highest oxygen radical absorption capacity (ORAC), followed by dried, frozen and canned cherries [34]. ORAC is a measure of the ability of antioxidants to neutralize free radicals whereby the higher the ORAC value, the stronger the antioxidant capacity of a particular antioxidant or food [35]. It is widely known that both sweet and tart cherries contain large amounts of anthocyanins and polyphenols but the comparison data of both cherries using similar analysis methods such as ORAC and ferric reducing ability of plasma (FRAP) assays are limited.

Quercetin, is another member of the phenolic flavonoid family other than anthocyanins [33] and is found in many fruits including cherries. According to the United States Department of Agriculture (USDA) database, tart cherry powder has the highest quercetin content among the rest of cherry products [36]. The antioxidant and anti-inflammatory properties of quercetin have been well studied, and there is a possibility that other compounds from cherries may have favourable properties for the treatment of gout [37].

Apple

Apple is an edible fruit produced by an apple tree (scientifically known as *Malus domestica*), is the most widely planted tree fruit around the world (covering about 5 million hectares and with a production of more than 75 million tonnes) due to its ability to adapt with diversity of climate[38 – 39]. Commonly top apple cultivars are "Red Delicious," "Golden Delicious," "Granny Smith," "Gala," and "Fuji" [40]. The largest apple producer is China which produced around 37 million tonnes a year, followed by USA (4.1), Turkey (2.9), Poland (2.9), India (2.2), Italy (2.4) and France (1.9)[41]. Apple has the taxonomic classification in the kingdom of Plantae, division of Magnoliophyta, class of Magnoliopsida, order of Rosales, family of Rosaceae, genus of *Malus* and species of *M. Domestica* [38].

The old saying "an apple a day keeps the doctor away" have been told from a generation to another generation probably because the apple is one of the fruits with various health benefits and must be consumed in a healthy diet plan. Apple have been known to have various beneficial phytochemical constituent that can reduce disease risk such as cardiovascular disease, cancer, asthma, and diabetes [42 – 43]. The whole apple fruit is edible except its seeds. Commercial products from apple fruit are apple cider, apple juice, jams, compotes, tea, wine, and dry apples. The whole apple fruit (including pulp, peels, and seeds) have been studied by many researchers due to large number of bioactive substances present. Apple is a nutritious fruit containing carbohydrates, sugar, fat, protein, and vitamins (A, B & C) [41]. In the European and USA, apple have been used as a major source for polyphenols in people's diet [44]. There are two main subtypes of polyphenols in apple which are flavonoids and phenolic acid [43]. It has been reported that twenty two percent of the phenolic compounds consumed from fruits are mainly from apple which makes them the largest source of phenolics compared to the other fruits [44]. In apple, the most important flavonoids are quercetins, catechin, epicatechin and their oligomers (proanthocyanidins) and these flavonoids are the one that responsible for astringency and bitterness of the apple. Meanwhile, the phenolic compound that are commonly found in apple are caffeic acid, *p*-coumaric acid and dihydrochalcones (phloretin glycosides) [43,45&46].

Despite of various phytochemicals and benefits by consuming apple, it has been reported that the apple (as well as apple juice, apple pomace and apple vinegar) has also a potential in treating the gout by neutralizing the uric acid as well as preventing the inflammation. Hecke et al., in 2006 [47] reported that the malic acid in apple can dissolves the uric acid and can helps relief when someone suffers from gout or rheumatism. In recent study, it has been reported that cysteine, malic acid, and arginine present in apple are considered appropriate to remove the stored toxic substance out from the body and found to be effective against gout, uric acid, urticaria, and treatment of kidney-related diseases [48]. In the same study it also reported that the triterpene acids such as chlorogenic acid, pomolic acid and maslinic acid have potential in anti-inflammatory and anti-arthritic effects via nuclear factor kappa beta (NF- kB) inactivation [48].

Pineapple

Pineapple (scientifically known as *Ananas comosus* L. Merr.) belongs to the member of Bromeliaceae family with about 45 genera and 2000 species and originated from South America [49–50]. Being discovered first by Europeans in 1493 on the Caribbean Island, this monocotyledonous plant is the only one grown commercially in Bromeliad family owing to its ability in producing edible fruits [48]. Pineapple has the taxonomic classification in the kingdom of Plantae, division of Magnoliophyta, class of Magnoliopsida, order of Poales, family of Bromeliaceae, subfamily of Bromelioideae, genus of *Ananas* and species of *A. comosus* [50]. Approximately 28.3 million tons of pineapples

are produced globally (over 20% of the world production), ranking it third in tropical fruit production after banana and citrus fruits [51 – 52]. For instance, the world-leading pineapple producers are Costa Rica, Philippines, and Brazil [53 – 54]. The bulk of the world's pineapple crop can be discovered throughout the tropics and subtropics due to the temperate climate (16° to 33°C) and rainfall distribution (650-3800 mm) [50]. In Malaysia, these perennial fruit-bearing tropical plants are highly demanded in the domestic market, specializing in generating quality canned pineapple with golden yellow colour [55].

Pineapple has its potential uses as a functional food and various pineapple-based products. The fusion of floral parts in the tree developed a non-climacteric pineapple fruit, and it is ubiquitous for its nutritional and beneficial values. It can be consumed fresh, dehydrated, canned, in juice and jams [56]. This delicious tropical fruit also is eaten alongside savoury cuisines such as chicken, ham, or beef. Apart from the fruit, various parts of the pineapple plant may also be utilised, such as pineapple leaf fibre, which has attractive textile fibre properties and is acceptable for fashion garments [57]. Likewise, one local study revealed the potential use of pineapple leaves in the green technology field, an alternative pulp in the paper-making industry [58].

Due to the high recognition of pineapples' medicinal purposes and food value, this well-known tropical plant has been used for centuries. The nutritional benefits of pineapples are as appealing as their distinctive anatomy. Several studies reported that the bioactive component in pineapple accountable for its anti-inflammatory activity in which the components involved included proteins, flavonoids (bromelain), tannins, carbohydrates, glycosides, and phenols. [59 - 62]. A wide range of therapeutic benefits has been attributed to pineapple due to the presence of cysteine proteases enzyme known as bromelain [49 & 64]. This valuable proteolytic enzyme can be either extracted from the fruit (standard coding: EC 3.4.22.33) or stem (standard coding: EC 3.4.22.32) [65]. Bromelain comprises peroxidase, acid phosphatase, several proteases inhibitors, and organically bound calcium, which possesses anti-inflammatory properties via blockage of kinins formation [66]. In gout management, experimental evidence suggested that bromelain play a part in reducing the uric acid level. It will cause the decomposition of urate crystal, thus relieving the pain associated with gout [67 – 68]. In short, bromelain acts as an anti-inflammatory which is proposed to be mediated via retardation of prostaglandin E2 (PGE-2) and COX-II synthesis [49]. As a result, the inhibition of pro-inflammatory mediators may lessen the nociceptive perception of pain in gout patients [69].

In addition to its treasured sensorial characteristics (flavour and aroma), this parthenocarpic plant is packed with a considerable number of vitamins such as vitamin C and β-carotene. Besides, catechin, epicatechin, and sinapinic acids were the predominant phenolic compounds that existed in pineapple [70 – 73]. Its prominent levels of vitamin C, β-carotene and the phenolic compound have long been linked with unique health-supportive properties. One local research that envisaged the antioxidant activities of pineapple extracts discovered that the number of phenolics present might provide a reliable source of antioxidants [74]. For instance, the high vitamin C content that demonstrated antioxidant characteristics may also protect healthy cells against free radicals. The role of vitamin C in the regulation of total oxidative stress and diminishing the concentration of ROS from the superoxide metabolic end products in XO activity contribute to its significant clinical effects in gout treatment [75 – 78]. Apart from the fruit extract, the other parts of pineapple may be essential in gout treatment. For instance, tacorin found in the pineapple stem is reported with health-related properties. This secondary metabolite protects the progression of inflammation via suppression of TNF-α level and promotes wound healing. The mechanism is

essential as gout patients are more likely to be predisposed to impaired wound healing, as proven in Rahayu et al., (2017) [79], the recovery progress of a wound in a group of rats treated with tacorin was faster than in an untreated group [79 – 81].

Sugar apple

Annona squamosa L. (Annonaceae), also called as sugar apple is a family of flowering plants consisting of trees, shrubs or rarely lianas have vast acceptance and traditionally been used in folk medicine and edible as food sources. The family of this plant is primarily found in the tropics, with only a few species found in colder climates. There are around 900 Neotropical species, 450 Afrotropical species, and the remaining species are Indo-Malayan [82]. Sugar apple is native to tropical South America and the West Indies however some other researchers claim that the sugar apple originated in the lowlands of Central America, where it is native, and was then spread throughout tropical America [83].

Some studies have shown that different parts of the plants are considered beneficial for various diseases [84 – 86]. The tribal men who lived in and around the villages of Aligarh district, which is in the state of Uttar Pradesh, India, and the people of Chotanagpur district, which is in the state of Bihar, India, used the young leaves of sugar apple extensively due to its anti-diabetic activity [88]. In the Aligarh district, locals used to take a mixture of 4 to 5 freshly grown young leaves and roughly 5 grains of black pepper first thing in the morning to treat diabetes, with ongoing therapy ensuring up to 80% favourable results. The treatment was especially popular in the Lodha society, where the plant was considered a sacred fruit. Previous ethnobotanical study also reported that sugar apple leaves are crushed and used to treat wounds, ulcers, hysteria, and fainting spells. Decocted leaves are used as a tonic, febrifuge, and cold treatment to cure dysentery. Unripe fruit was used to treat diarrhoea, whereas crushed ripe fruit was used to treat surface tumours. Diarrhoea and dysentery were treated with the stem bark and root [87]. A potential compound could be obtained from medicinal plants. Therefore, attention in recent times has been focused on the isolation, characterisation, and utilisation of anti-hyperuricaemia natural. Many Indonesian medicinal plants have been used for the preventing and gout treatment and related with an inflammatory disorder, but they still lack sufficient scientific evidence. In addition, sugar apple also has been used traditionally by the local people in Indonesian for gout treatment, rheumatic, and cancer [9].

Numerous studies have shown that these plants have a wide spectrum of pharmacological characteristics when being eaten such as antibacterial activity, antidiabetic activity, antihyperlipidemic activity, antioxidant activity, antitumour activity and anti-gout activity [9,88]. The findings of anti-gout activity are attributed by the antihyperuricemic activity and inhibition of XO activity that belong to the ethanol leaves extracts of the sugar apple, analgesic and anti-inflammatory activity of ether extract from the bark of sugar apple [9,85].

In vitro, in vivo **and Clinical trials**

Cherry

A recent study was conducted by Li et al. (2020) [98] to investigate the effect of different doses of cherry powder on SUA in hyperuricaemic induced rat models. They also compared the effects of cherry powder and AP on secondary kidney and hepatic injury in the rat models. The findings revealed that low doses of tart cherry powder (0.17 g/kg body weight) had slightly lowered the SUA and improved kidney damage, while a high dose of it (0.50 g/kg body weight) could barely relieve kidney damage. Indirectly, it can be said that low-dose tart cherry powder has limited improving effect on SUA. Another

interesting finding from this study was that the low dose tart cherry powder reduction of SUA was more associated with adenosine deaminase activity (ADA) rather than the common XO activity [98].

Recent studies have found out that after consuming cherries and cherry products, SUA levels of healthy individuals were noted to be significantly reduced. In addition, consumption of cherry juice had also proven to lower SUA in participants who were overweight or obese [99 – 100]. The bioactive component in cherries that may be accountable for these effects is ambiguous. However, Bell et al., in 2014 [99] proposed that anthocyanins and/or other phenolic compounds present in cherry may be the principal cause. There are not many reported studies involving patients with gout. In a case cross-over study by Zhang et al., in 2012 [101] which involved 633 patients with gout, it was found out that consumption of cherries was associated with a 35 % reduction in the risk of gout attacks. The study was based on the acute temporal relationship between the consumption of cherries and the likelihood of gout. It was reported that after 2-days consumption of cherries, the risk of gout attacks was significantly reduced. Cherry juice and cherry extract gave consistent results across groups which was classified by gender, status of obesity, purine intake, alcohol intake, diuretic use, and gout medication. They also reported that complementary use of AP with cherries can reduce the risk of gout attacks [101].

Meanwhile, in another study utilising internet survey involving patients with history of gout by Singh et al., (2015) [102], few outcomes related to the consumption of cherry related supplements were reported. Firstly, it was found out that the number of gout attacks was significantly reduced. Secondly, the possibility of gout attacks was lower. Thirdly, a trend towards a lower proportion with a ULT drug possession rate of 80 % was observed and lastly, compared with the previous month, the number of days without ULT has increased. The findings reported by this study was in comparison with the previous month [102]. On the other hand, one of the recent studies done by Martin & Coles, in 2019 [102] focused on the overweight and obese group of people. They reported that after taking tart cherry juice every day for 4 weeks, SUA levels were found significantly reduced by 19.2%. The results can give an insight that tart cherry juice may be beneficial in the treatment of hyperuricaemia or to be practiced in those with gouty arthritis [102]. Apart from that, three pilot studies were conducted by Schlesinger, in 2012 [103] to examine the effect of concentrated cherry juice on gout prophylaxis in which one of them was included in this review. The study found out that both cherry and pomegranate juice had caused slight reduction in plasma uric acid levels however, the effect by cherry juice was less obvious. Nevertheless, none of the observed changes reached a significant level [103].

A study was conducted which examined the relationship between cherry consumption with uric acid levels in 12 healthy participants whereby the outcome was measured after a shorter time period (2 hours) and involved the consumption of Montmorency cherry as compared to previous study. The result revealed that a significant decrease in SUA levels was observed following cherry consumption in volunteers [101]. Despite showing promising potential as an agent to reduce SUA, the most recent study found out that cherry concentrate in 4 different doses (7.5, 15, 22.5 or 30 ml twice a day) had no significant effect in reducing SUA over 28 days. It is also stated that concentration of cherry had no significant in reducing the frequency of gout flares. In fact, there were 24 reported cases of adverse effects from the findings [104].

Apple

The study regarding the potential of apple and its derivatives products in treatment of gout is not as many as the other fruits. In 2010, Choi et al., [105] reported that consumption of apple juice,

grapefruit juice, tomato juice and others did not associate with a higher incidence of gout as compared to the orange juice [105]. However, a study reported that consumption of apple pomace causes the increase of plasma uric acid due to the presence of fructose [106]. Fructose have been reported by several study to be one of the precursors that causes the elevation of the uric acid via degradation of adenosine triphosphate (ATP) to adenosine monophosphate (AMP) in which later degraded into uric acid [107 – 108]. Uric acid possesses antioxidant activity which was suspected to result in the augmentation of plasma antioxidant potential after apple or apple juice consumption. Godycki-Cwirko et al. reported in 2010[109] that the amount of circulating polyphenols increased by apple consumption appeared to be too low to be the key factor responsible for the rise of plasma antioxidant capacity [109]. Nevertheless, despite the negative effects of fructose contains in apple pomace, an *in vitro* study conducted previously by Nile et al., in 2019 [107] which analysed the different types of apple pomace extracts as an inhibitor for XO enzyme using High Performance Liquid-Chromatography Mass Spectrometer (HPLC-MS/MS) [110]. The result obtained was all apple pomace extracts contains high phenolic compounds and possess good XO inhibitory effects *in vitro* in which the most effective inhibitor was recorded by the methanol fraction (IC50 value, 19.6 ± 0.11 μg/mL) followed by ethanol extracts (24.1 ± 0.18 μg/mL), ethyl acetate (28.8 ± 0.15 μg/mL), chloroform (36.2 ± 0.14 μg/mL), and n-hexane (42.5 ± 0.10 μg/mL). However, the effectiveness of the apple pomace extracts as the XO inhibitor was not as efficient as AP (positive control with IC50 9.6 ± 0.04 μg/mL).

The amount of p-coumaric acid is largely present in several fruits such as apples, oranges, grapes, tomatoes, potatoes, and spinach [111]. Previously, a study was investigated the ability of p-Coumaric acid in reducing the expression of TNF-α in the *in vivo* study using adjuvant-induced arthritis rat model. The anti-inflammatory effects of p-coumaric acid (100 mg/kg body weight) were determined by using the immunofluorescence confocal microscopy and circulating immune complexes in serum of adjuvant induced arthritic rats in order to examine its effect on expression of TNF-α in synovial tissue. The result obtained was that the cell mediated immune response was increased and the macrophage phagocytic index seen in control rats were significantly reduced ($p<0.05$) after treated with p-coumaric acid, indicating an immunosuppressive property, whereas serum immunoglobulin levels were found to be increased in p-coumaric acid treated control rats. The p-coumaric acid also significantly ($p<0.05$) possesss the anti-inflammatory effects in adjuvant-induced arthritic rats by ability to decrease the expression of inflammatory mediator TNF-α and circulating immune complexes [112].

Another study reported on the anti-inflammation activity of apple polyphenols via *in-vivo* gout Wistar rat's model. The inflammation rate was determined by the swelling rate of joint as well as determining the level of Myeloperoxidase (MPO) activity. During inflammation occur in gout, MPO was being released, and the level of MPO in systemic circulation can be used to determine the index of infiltration of neutrophil. Furthermore, in this stage, some reactive intermediates formed by MPO catalysed reactions may modify signalling mediators which can lead to in cellular signalling [101 & 104]. Based on the result obtained, the joint swelling rate decrease within 72 hours from 32.14 %±2.40 10.59 %±2.54 in rats group treated with apple polyphenol and the result obtained was significantly different when compare with the control. Moreover, apple polyphenol proven to restrain the MPO activity and possess an effective role as anti-inflammation in gout rat's model.

A study reported previously which conducted a randomized, double-blind, placebo-controlled clinical trial to study on the effect of polyphenols

containing in apple towards uric acid as well as to compare with the standard anti-hyperuricaemia agent, AP. The study involved 62 overweight subjects which were randomized with daily oral intake of 300 mg of apple polyphenols or placebo for two months. The result revealed that those treated with polyphenols significantly reduced uric acid level and had a protective effect against vascular oxidative stress (OS), probably via the inhibition of the enzyme XO [113 – 115].

Pineapple

Several kinds of research had been conducted to substantiate the putative therapeutic actions of bioactive compounds of pineapple in treating gout. One study looked at how consumption of pineapple enriched foods in hyperuricaemic rats affected the uric acid level in experimental animals. It was noted that a hyperuricaemic rat group that consumed 10% and 20% fortified pineapple cake showed a non-significant increase in SUA compared to the control group. The author concluded that pineapple consumption decreased uric acid levels in hyperuricaemic rats [116]. The outcome was in line with a pre-experimental study conducted by Fadlilah et al., in 2021 [67] among 13 elderly who suffer from arthritis gout. The authors observed the uricosuric effect post-consumption of pineapple juice for seven days, whereby the average acid content value of the elderly is reduced from 8.7 mg/dl to 7.1 mg/dl (p-value = 0.000) after consuming pineapple juice. The researchers claimed the need for pineapple intake in the patient with arthritis gout due to vitamin C's role in eliminating uric acid via urine [67]. The studies mentioned above are in agreement with the findings from a meta-analysis of randomized controlled trials assessing the effect of vitamin C on SUA levels. The combined effect of the pooled trials showed that vitamin C significantly lowered uric acid by -0.35 mg/dl (95% CI [-0.66, -0.03] (P = 0.032) [117]. In addition, one recent double-blind, randomized, placebo-controlled clinical trial linked the association of a nutraceutical product containing bromelain with a reduction of uricaemia and high-sensitivity C-reactive protein (Hs-CRP) in the interventional group as compared to baseline and placebo ($p < 0.05$) [118]. This study was also consistent with the previous study's recommendation. The authors suggested pineapple as an approach to lower blood uric acid levels, given that 90.5% of the participants in the research reported experiencing declination of uric acid levels post-ingestion of pineapple [68].

Inflammation is pivotal in the development of gout. The contention of bromelain in easing the gout symptoms had been well-documented by some studies. One of the earliest studies from Cohen & Goldman (1964) reported that practically 75% of moderate-to-severe arthritis patients recruited in the study experienced either complete or near-total lessening of swelling after the bromelain treatment. The finding was also associated with a corresponding decrease in pain and soreness following bromelain administration (60 to 160 mg per day) [119]. The anti-inflammatory and analgesic properties exerted by this enzyme also had been proven by Walker et al., (2002) [120]. The authors concluded that the bromelain might alleviate pain in a dose-dependent manner post-30-day intervention in 77 healthy adults with bromelain. The study's volunteers were being allocated with either 200 mg or 400 mg per day at random, reported to improve the primary study outcome– the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) knee health Index significantly [120].

Similarly, this study is supported by a multicenter, observational, prospective, open-label survey published in 2014. The research revealed that the reduction of joint pain was clinically relevant in patients treated with bromelain-containing nutraceuticals in the conjugation of other plants. Overall, out of 42 patients suffering from acute or chronic, degenerative spine or joint pain, most of them attained the degree of pain defined as patient acceptable symptom state (PASS) [121]. Despite promising results obtained, the significance is

limited by the lack of investigating a single product at a time. Besides, some research identified the enzymatic compound as an excellent alternative to the typical NSAIDs, exhibiting promising efficacy and a better safety profile [119,122 – 122]. However, there is limited evidence available on the usage of bromelain in the children population and its efficacy at higher concentrations. More well-designed trials are warranted to discover the knowledge gap to establish the effectiveness and optimum dosage for bromelain. It is essentially necessary to elucidate further its clinical potential [63].

Sugar apple

Previous *in vivo* and *in vitro* studies showed that sugar apple was significantly possess XO inhibition and able to reduce SUA level in oxonate-induce rats [125]. The parts and solvent that are commonly used are leaves, methanol, and ethanol respectively, with the dose of the extract ranging between 75 – 400 mg/kg of body weight [126]. The bioactive compounds in sugar apple which were identified through phytochemical screening that may be accountable for these effects are alkaloid, phenolic, tannin, and flavonoid. Similarly, several investigations have shown that flavonoid compounds have XO inhibitory properties [124 – 125]. These statements were further supported and in line with the study done by Cos et al. in 1998, where they looked at the structure-activity relationship of flavonoids as XO inhibitors and superoxide radical scavengers produced by the enzyme XO [125]. However, the study shown a slightly contrary finding from what has been found by Nagao et al. in 1999, where flavones demonstrated slightly higher inhibitory effect of XO activity than flavonols. Nagao et al. in 1999 concluded that a wide range of dietary flavonoid has the inhibitory effect on XO activity. Among them, the planar flavones and flavonols with a 7-hydroxyl group had a great inhibitory effect on XO activity. Therefore, it has been put into a perception that the specific mechanism for inhibition and the *in vivo* effect of these flavonoids on oxidative injury and urate accumulation by XO should be studied further to safely justify the roles of dietary flavonoids in human health and wellbeing [124]. In addition, Alvionita et al. in 2019 [95] also reported that flavonoid isolated from 275 grams flesh of sugar apple exhibited the greater inhibition activity toward XO compared to allopurinol (AP) and has a potential to be developed as antigout agent [95].

It is known that hyperuricaemia is associated with the formation of urate crystals in the joints which causing gout, and in the kidney, predisposes to urate nephrolithiasis [89 – 90]. The sugar apple extracts at a dose of 75 mg/kg significantly reduced uric acid level in oxonate-induce male Wistar rats after 1-hour oral administration. The extracts also were evaluated by the xanthine-XO enzymatic system to identify the XO inhibitory activity. It was found that ethanolic extracts of sugar apple were exhibited less inhibitor effect on XO activity *in vitro* assay [9].

Furthermore, gout is clinically described as inflammatory arthritis caused by crystals of MSU interacting with tissue during purine breakdown by the enzyme XO [91 – 92]. The oxidative hydroxylation of hypoxanthine to xanthine to uric acid is catalysed by XO, resulting in severe inflammation [93]. It was found that sugar apple bark extracts containing unsaponified petroleum ether extract and caryophyllene oxide were playing a remarkable role as analgesic and anti-inflammatory properties. The sugar apple extract at the dosage level of about 12.5 mg/kg, 25 mg/kg and 50 mg/kg demonstrated a significant central as well as peripheral analgesic and anti-inflammatory activity in the Albino rats of Wistar after 1-hour oral administration [94].

The previous experimental procedure on ethanol extract of sugar apple was carried out that showed flavonoids' presence [95]. The *in vitro* XO inhibitory test and *in silico* analysis test were performed to determine how many enzymes activity in forming uric acid with and without the

addition of inhibitors and to predict the ability of this flavonoid compound to inhibit the XO enzyme relative to AP based on their binding affinity, respectively. Significantly, both tests show positive outcomes where the ethanol extract of sugar apple caused a greater decrease of XO activity compared to the addition of AP. It was also confirmed that quercetin-3-glucoside (one of the flavonoids) has a greater affinity toward the other two (2) ligands, which are xanthine and AP, respectively. Therefore, flavonoid isolates from ethanol extract of sugar apple showed higher inhibitory action against XO *in vitro* and in silico than the AP, suggesting that the flavonoid isolate has a high potential as an antigout drug [97].
Moreover, many studies also indicated that flavonoid compounds had XO inhibitor activity and anti-hyperuricemia in an animal model [96 – 97]. Six (6) of fifteen (15) flavonoids, which are quercetin, morin, myricetin, kaempferol, apigenin and puerarin, were confirmed to possess strong hypouricemic actions in hyperuricemic mice both at 50 and 100 mg/kg. Luteolin, formonoetin, naringenin, and daidzin exhibited a significant hypouricaemic effect just at 100 mg/kg, while genistein, baicalin, naringin dihydrochalcone and silibinin had no effects [98].

To date, there are extremely limited studies performed using plant-based drugs to determine the efficacy of sugar apple in the treatment of gout. However, there is a study reported that the other genus of Annonaceae family, which refers to *Annona Muricata* L. leaves have an impact on reduction of uric acid level of their study population [126]. It was found that the prepared soursop juice (*Annona Muricata* L. leaves) contained Vitamin C that act as an antioxidant which was effective in reducing uric acid level. This study showed a promising result of Annonaceae family. Thus, further investigation is required to determine the effectiveness of sugar apples in reducing uric acid levels in patients with gout. Even though there is enough evidence from *in vitro* and *in vivo* studies on sugar apples, clinical trials are still needed to determine the specific effects of sugar apple extracts on human health [127]. Therefore, there is a need to investigate natural XO inhibitors, particularly in *in vivo* studies, clinical studies, active compound discovery, plant safety, and pharmacokinetic and bioavailability studies. A summary of the potential fruits for gout therapy is shown in Table 1.

Future Prospect

The common treatment of gout includes the pharmacological and non-pharmacological aspects. Due to drug interactions, drug toxicity and potential polypharmacy in patients with multiple diseases, conventional drugs for patients with gout are limited. Diet therapy and modification can reduce uric acid levels, delay the complications of gout, and may contribute to the reduction or removal of conventional medications. There is strong evidence that diet is the most changeable factor in the treatment of gout [127-128]. In terms of non-pharmacological treatment, patients are usually advised to adjust their diet by reducing alcohol intake and avoiding high purine foods and dairy products as they were proven to be linked to higher risk of gout flares and increased uric acid. However, this is easier said than done. Since majority of the foods people consume daily are seafoods and red meat, diet modification often ends in vain for most people. Meanwhile, the pharmacological treatment consists of XO inhibitors, NSAIDs, corticosteroids and probenecid to treat gout. Pharmacological treatments however, often present with side effects in which most of the time are minor and tolerable but may affect the level of adherence especially in the elderly. This issue is even worse in patients with other comorbidities and receiving various classes of drugs. Older people tend to get confused with the use and administration of each medication which may lead to poor compliance. Consuming too many medications at one time may also contribute to pill burden which can open the barrier to ULT compliance. Since the majority of previous

studies, especially those with larger sample sizes, have proven the efficacy of cherry, apple, pineapple and sugar apple fruit in reducing SUA, these fruits can be commercialised further and given to patients with gout as an adjunct treatment or alternatives to their pharmacotherapy regimen. These fruits can be made into medicinal beverages such as tea and add-on to patients' gout treatment [67,95,108&114–115]. Even if they forget to take their medications, improvement in uric acid level can be expected if they consume their medicated drinks.

Cherry has been commercialised into juice and capsules. Some people drink cherry blend to reduce their uric acid levels and lowers risk of gout attacks. In future, tart and sour cherry may also be developed into medicinal tea drinks. Meanwhile, apple has also been successfully marketed as products related to gout therapy. There are abundant of apple products made available such as juice, dried and even apple cider vinegar which is made from fermented apple products. As for sugar apple fruit, it can be processed and made into medicinal tea.

Currently, the modern technology is not yet able to process pineapple efficiently leading to low productivity and adversely affecting the technical infrastructure. For this reason, various efforts have been taken to improve production efficiency and increase fruit yield and quality through various development programs. It is known that pineapple co-products are high in fibre and they are rich in polyphenol compounds and antioxidants [132]. Therefore, pineapple co-products should be recognised as a potential source of nutrition. Not to forget, pineapple may serve as low-cost alternatives for health-related purposes and improving health in general. More study to incorporate pineapple and other fruits like cherry, apple and sugar apple fruit need to be conducted in order to maximise their benefit in the management of gout and minimise the risk to consumers [133].

Conclusion

Drug interactions, drug toxicity and polypharmacy in patients with multiple co-morbids has limited the use of conventional drugs for patients with gout. European Alliance of Associations for Rheumatology (EULAR) has recommended lifestyle advice for all gout patients, including dietary intervention. Keeping this in mind, researchers are gaining new interest in exploring natural sources as alternative medicine. It is a mutual faith that everything that occurs in nature has beneficial effects. Several plants are reported with various medicinal properties and are used in practice nowadays. The same applies to cherry, apple, pineapple and sugar apple. They may become the source of therapeutic agents in treating gout, which can be easily found and consumed. The complexity of these fruits is accounted for by several nutrients existing, such as flavonoids and phenols (quercetins, catechin, epicatechin, anthocyanin, malic acids and etc), proteins, and vitamins (A, B and C). These four potential fruits have been shown to reduce uric acids as well as inflammation to promote healing in gout and can be developed as a future therapy for better outcomes in gout. Of the four fruit candidates mentioned in the review, cherries show more promising potential for treating gout than others. Despite its tiny size, this nutrient-rich fruit is deemed to be a reliable non-pharmacotherapeutic option for gout.

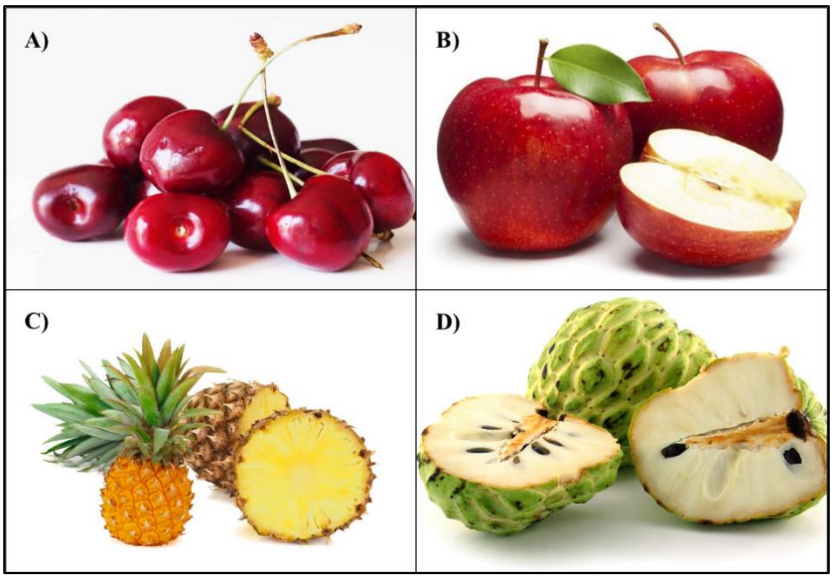

Figure 1. Potential fruits as gout therapy; A) Cherry, B) Apple, C) Pineapple and D) Sugar apple

Table 1. Phytochemical compound contains in fruits and its products that are potential for gout therapy

Fruits	Fruit's product	Phytochemical constituent	Potential Applications and Findings	References
Cherry	Whole fruit	Vitamin C	The risk of gout attacks tend to decrease with increasing cherry consumption up to 3 servings over 2 days however, further intake did not appear to provide a greater protective effect. Cherry extract intake was associated with a 45% lower risk of gout attacks.	Zhang et al., 2012 [101]
	Cherry juice	Anthocyanins	Cherries contain natural COX-I and COX-II inhibitors. The COX inhibitory activities of anthocyanins from cherries were comparable to those of ibuprofen and naproxen used in treatment of gout. In addition, anthocyanins extracted from cherries have shown anti-inflammatory properties, via scavenging of the reactive nitric oxide radical.	Schlesinger, 2012 [103]
			Systemic inflammation as indicated by hsCRP was reduced following both doses of the concentrate.	Bell et al., 2014 [99]
		Polyphenols	Tart cherry juice consumption can reduce SUA that is hyperuricemia, and may be useful in those individuals prone to gouty arthritis or other proinflammatory conditions.	Martin & Coles, 2019 [100]
	Cherry powder	-	Reduction of SUA at low dose through reduction of ADA activity and alleviation of kidney injury.	Li et al., 2020 [98]
Apple	Apple pomace	Phenolic	Act as an inhibitor for XO enzyme for preventing uric acids formation.	Nile et al., 2019 [110]
	Whole fruit	p-coumaric acid	The p-coumaric possess the anti-inflammatory effects in adjuvant-induced arthritic rats by ability to decrease the expression of inflammatory mediator TNF-α and circulating immune complexes.	Pragasam et al., 2013 [112]
		Polyphenols	Anti-inflammatory and uricosuric effect: • The apple polyphenol proven to possess an effective role as anti-inflammation in gout rat's model by ability in restraining the MPO activity. • The apple's polyphenols significantly reduced uric acid level and had a protective effect against vascular OS via the inhibition of the enzyme XO.	Stamp et al., 2014 [111] ; Zhang 2012 [108]Cicero, 2017 [114]; Roumeliotis , 2019 [115]
Pineapple	Whole fruit	Vitamin C	Uricosuric effect: • Hyperuricaemic rat group that consumed 10% and 20% fortified pineapple cake showed a non-significant increase in SUA compared to the control group • The average acid content value of the elderly is reduced from 8.7 mg/dl to 7.1 mg/dl (p-value=0.000) after consuming pineapple juice • 90.5% of the participants in the research reported experiencing declination of uric acid levels post-ingestion of pineapple.	Al Tamim, 2014 [116] Fadlilah et al., 2021 [67] Sevilia & Dwiningtyas, 2016 [68]
		Bromelain	Anti-inflammatory and analgesic properties by improving the primary study outcome the WOMAC knee health Index significantly. Plus, most of the respondent attained the degree of pain defined as PASS.	Walker et al., 2002 [120] ; Conrozier, 2014 [121]
Sugar apple	Leaves	Flavonoids	Act as antihyperuricaemic agent by reducing the uric acid level in oxonate-induce male Wistar rats after 1-hour oral administration. Also act as XO inhibitor by reducing the uric acid level due to inhibitory effect on XO activity.	Sunarni et al., 2015 [9]
	Whole fruit (flesh)	Flavonoids	It has a great potency as XO inhibitor by decreasing the XO activity at both, *in vitro* and in silico analysis method.	Alvionita et al., 2019 [95]

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