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FULL PAPER

Anti-gout potential of selected edible flowers

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Abstract

Gout is a form of inflammatory arthritis triggered by the interaction between monosodium urate crystals and tissues during the purine metabolism by xanthine oxidase. This study aimed to determine the xanthine oxidase inhibitory activity, total phenolic content, total flavonoid content and total anthocyanin content of 10 selected edible flowers, namely *Rosa* sp., *Malus* sp., *Lavandula* sp., *Lilium* sp., *Hibiscus sabdariffa* L., *Chrysanthemum* sp., *Matricaria* sp., *Gomphrena* sp., *Myosotis* sp. and *Jasminum* sp. extracted using hot water infusion method. Phytochemical contents and the anti-gout activity of the flower extracts using the xanthine oxidase inhibition assay were determined spectrophotometrically. The results revealed that three aqueous flower extracts (*Rosa* sp., *Hibiscus sabdariffa* L. and *Malus* sp.) exhibited potent xanthine oxidase inhibitory activity (IC_{50} values, 0.10±0.15 µg/mL, 0.12±0.11 µg/mL and 2.59±3.8 µg/mL, respectively), which were comparable to the positive control, allopurinol (IC_{50} value, 4.9±0.00 µg/mL). The highest phenolic and flavonoid contents were found in *Lavandula* sp. (4.39±0.13 mg GAE/g and 63.46±1.07 mg RE/g) while *Rosa* sp. showed the highest content of anthocyanin (70.14±4.82 mg c-3-gE/g). Positive correlations were observed between the phytochemicals and xanthine oxidase inhibitory activity of the flower extracts. Hence, this study suggests that *Rosa* sp., *Hibiscus sabdariffa* L. and *Malus* sp. possess anti-gout potential, which is associated with the presence of possible anti-gout phytochemicals. The isolation of the bioactive compounds that exhibit significant anti-gout activity among the selected flowers is recommended for future research.

1. Introduction

Gout is a type of arthritis associated with joint pain and swelling which occurs due to the increase of uric acid in the blood. Xanthine oxidase is an enzyme that controls the uric acid level by catalyzing the oxidative hydroxylation of hypoxanthine to xanthine, then to uric acid (Abu Bakar *et al*., 2018). The inflammation response is initiated with the formation of monosodium urate crystals at the joints and tissues under abnormally high uric acid levels as a consequence of gout development (Abu Bakar *et al*., 2018). Allopurinol is the most common drug used for gout treatment and acts as a xanthine oxidase inhibitor, but it causes several side effects including acute renal and hepatic failure, gastrointestinal distress, hypersensitivity reactions and skin rash (Chen *et al*., 2005; Pacher *et al*., 2006). Hence, searching for novel xanthine oxidase inhibitors with greater therapeutic potential and fewer side effects is highly needed.

There is a vast array of natural products potentially to be developed as xanthine oxidase inhibitors, at present, the research related to this discovery is still largely unexplored (Hudaib *et al*., 2011). Flower and herbal tea infusions have been gaining popularity among researchers due to their nutritional value and therapeutic importance. In addition, refreshing tea infusions made from the pure or powdered forms of flowers are popular due to their fragrance, antioxidant properties and therapeutic applications (Aoshima *et al*., 2007). Its taste, aroma and health benefits also contribute to increased attention and interest for flower teas consumption (Hussain *et al*., 2019).

Phenolics and flavonoids, including anthocyanins, are the most common phytochemicals found in edible flowers (Kumari *et al*., 2021). Phytochemical screening

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of plant extracts has revealed that these compounds may act as anti-gout agents by inhibiting the biosynthesis of uric acid and it is worthy of further research on other samples (Unno *et al*., 2004). Thus, this study aimed to evaluate the anti-gout activity and phytochemical contents such as phenolics, flavonoids and anthocyanins among the selected edible flowers.

2. Materials and methods

2.1 Chemicals and reagents

Gallic acid, rutin, allopurinol and xanthine substrate were purchased from Acros Organics (Fair Lawn, New Jersey, United States). Folin Ciocalteu reagent, aluminium chloride hexahydrate, sodium hydroxide, disodium hydrogen phosphate heptahydrate and potassium chloride were obtained from Merck (Darmstadt, Germany). Sodium carbonate and sodium nitrite were acquired from Fisher Scientific (Hampton, New Hampshire, United States). Xanthine oxidase from bovine milk, hydrochloric acid (0.5 M) and sodium phosphate monobasic was bought from Sigma-Aldrich (St. Louis, Missouri, United States).

2.2 Flowers selection and identification

A total of ten dried flowers, namely *Rosa* sp., *Malus* sp., *Lavandula* sp., *Lilium* sp., *Hibiscus sabdariffa* L., *Chrysanthemum* sp., *Matricaria* sp., *Gomphrena* sp., *Myosotis* sp. and *Jasminum* sp. were purchased in the marketplace at Jonker Walk, Malacca, Malaysia. Two main criteria were established for the sample selection; (1) plant parts used such as a flower in this case, and (2) anti-inflammatory properties of flowers based on the literature. All the flower samples were identified through the guidance of information such as plant morphological description, photographs and illustrations from the botanical databases. Next, the dried flowers were pulverized using a grinder (Panasonic, MX-GM1011H, Japan) and kept in the zip lock bags.

2.3 Extraction of flower

Each powdered flower (1 g) was mixed with 100 mL of boiling water for 3 mins (Abu Bakar *et al*., 2006). The solution was then filtered through the tea filter bag and left to cool down. The aqueous flower extract was used for further phytochemical content determination and anti -gout activity.

2.4 Phytochemical testing

2.4.1 Determination of total phenolic content

Total phenolic content was determined by Folin-Ciocalteu assay (Mohd Noor *et al*., 2020) using gallic acid as the standard. An amount of 0.9 mL of distilled water was mixed with 2 mL of ten-fold diluted Folin Ciocalteu reagent and 0.1 mL of aqueous flower extract. After 5 mins, a 2 mL of 7% (w/v) sodium carbonate solution was added to the mixture and incubated for 30 mins at room temperature. The absorbance values of the reaction mixtures were measured at 760 nm using T60 UV-Vis spectrophotometer (PG Instruments Limited, United Kingdom) and the results were expressed as mg gallic acid equivalent (GAE) per gram of flower sample.

2.4.2 Determination of total flavonoid content

Total flavonoid content was determined using the aluminium chloride colourimetric method (Ali Hassan and Abu Bakar, 2013) and rutin was used as the standard. An amount of 1 mL of aqueous flower extract was diluted with 4 mL of distilled water and then mixed with 0.3 mL of 5% sodium nitrite solution and 0.3 mL of 10% aluminium chloride hexahydrate. The mixture was kept for 5 mins. About 2 mL of 1 M sodium hydroxide was added to the mixture and mixed using a vortex mixer (Labmart, LM-3000, Malaysia). The absorbance values of the reaction mixtures were measured at 510 nm using a T60 UV-Vis spectrophotometer (PG Instruments Limited, United Kingdom). The results were expressed as mg rutin equivalent (RE) per gram of flower sample.

2.4.3 Determination of total anthocyanin content

Total anthocyanin content was determined using spectrophotometric pH differential protocol with some modification (Giusti and Wrolstad, 2001). A 3.5 mL of potassium chloride buffer (0.025 M; pH 1.0) was added into 0.5 mL of aqueous flower extract. The mixture was mixed using a vortex mixer (Labmart, LM-3000, Malaysia) and allowed to stand for 15 mins. The absorbance values of the reaction mixtures were measured at 515 nm and 700 nm against blank as distilled water using a T60 UV-Vis spectrophotometer (PG Instruments Limited, United Kingdom). The results were expressed as mg cyanidin-3glucoside equivalent (c-3-gE) per gram of flower sample.

2.5 Anti-gout activity

Xanthine oxidase inhibition assay is an enzyme assay used to determine the anti-gout activity of the plant extracts (Abu Bakar *et al*., 2020) and it was conducted based on the study of Unno *et al*. (2004) with some modifications. Allopurinol (100 µg/mL) was used as the positive control in this study. The inhibitory effect on xanthine oxidase was measured spectrophotometrically at 295 nm (Ahmad *et al*., 2006). The reaction mixture consisted of 0.3 mL of 50 mM sodium phosphate buffer (pH 7.5), 0.1 mL of flower extract or standard solution (10-100 µg/mL) dissolved in distilled water, 0.1 mL of freshly prepared enzyme solution (0.2 units/mL of XO in phosphate buffer) and 0.1 mL of distilled water. The

assay mixture was pre-incubated at 37°C for 15 mins. Then, a 0.2 mL of substrate solution (0.15 mM of xanthine) was added to the mixture. The reaction mixture was incubated at 37°C for 30 mins. Next, the reaction was stopped with the addition of 0.2 mL of 0.5 M hydrochloric acid. The absorbance values of the reaction mixtures were measured using a UV-VIS spectrophotometer (PG Instruments Limited, United Kingdom) against a blank prepared in the same way but the enzyme solution was replaced with the phosphate buffer. Another reaction mixture was prepared (control) having 0.1 mL of distilled water instead of test compounds in order to have maximum uric acid formation. The degree of xanthine oxidase inhibitory activity was evaluated according to equation (1) (Nessa *et al*., 2010):

$$Inhibition\ (\%) = (1 - \frac{B}{A}) \times 100 \quad (1)$$

Where A is the absorbance of the enzyme without extract and B is the absorbance of the enzyme with the extract. The half-maximal inhibitory concentration (IC_{50}) is defined as the concentration of the test samples required to inhibit 50% of the xanthine oxidase enzyme, which concomitantly decreases the uric acid production by 50% (Nessa *et al*., 2010). IC_{50} values were obtained through the slope of the plot of the percentage inhibition against various concentrations of samples.

2.6 Statistical analysis

All experiments were carried out in triplicate. The correlation analysis was done to evaluate the association between the phytochemicals and xanthine oxidase inhibitory activity using the Pearson correlation test.

3. Results and discussion

3.1 Phytochemical contents of the selected flowers

The total phenolic, flavonoid and anthocyanin contents in the selected flowers were determined in this study (Table 1). Overall, the total phenolic content of flower extracts ranged from 0.45±0.03 to 4.39±0.13 mg GAE/g. The highest phenolic content was observed in *Lavandula* sp. extract with the value of 4.39±0.13 mg GAE/g. The second and third highest phenolic contents were recorded in *Rosa* sp. (3.89±0.19 mg GAE/g) and *Malus* sp. (3.79±0.20 mg GAE/g), respectively, followed by *Chrysanthemum* sp. (2.88±0.23 mg GAE/g), *Myosotis* sp. (1.77±0.07 mg GAE/g), *Lilium* sp. (1.29±0.12 mg GAE/g), *Matricaria* sp. (0.89±0.09 mg GAE/g), *Hibiscus sabdariffa* L. (0.89±0.05 mg GAE/g), *Jasminum* sp. (0.71±0.04 mg GAE/g) and *Gomphrena* sp. (0.45±0.03 mg GAE/g).

Additionally, the range of total flavonoid content of flower extracts was within 2.56±0.58 to 63.46±1.07 mg RE/g. *Lavandula* sp. also showed the highest flavonoid content with the value of 63.46±1.07 mg RE/g. Total flavonoid contents of other flower extracts were shown in the descending order of *Chrysanthemum* sp. (52.19±0.20 mg RE/g), *Malus* sp. (28.69±0.13 mg RE/g), *Myosotis* sp. (15.85±1.65 mg RE/g), *Rosa* sp. (13.13±0.93 mg RE/g), *Hibiscus sabdariffa* L. (11.57±0.89 mg RE/g), *Matricaria* sp. (10.84±0.27 mg RE/g), *Lilium* sp. (8.87±1.03 mg RE/g), *Jasminum* sp. (8.68±1.08 mg RE/g) and *Gomphrena* sp. (2.56±0.58 mg RE/g).

The presence of anthocyanin was observed among the flower extracts with the range from 2.23±2.78 to 70.14±4.82 mg c-3-gE/g. The high anthocyanin contents were found in *Rosa* sp. with the value of 70.14±4.82 mg c-3-gE/g, followed by *Myosotis* sp. (34.51±18.18 mg c-3 -gE/g), *Lilium* sp. (26.05±2.00 mg c-3-gE/g), *Lavandula* sp. (22.93±5.19 82 mg c-3-gE/g), *Hibiscus sabdariffa* L. (8.91±1.39 mg c-3-gE/g), *Chrysanthemum* sp. (6.01±2.67 mg c-3-gE/g), *Matricaria* sp. (4.68±4.06 mg c-3-gE/g), *Malus* sp. (4.01±5.22 mg c-3-gE/g), *Gomphrena* sp. (3.79±2.04 mg c-3-gE/g) and *Jasminum* sp. (2.23±2.78 mg c-3-gE/g).

Phenolic, flavonoid and anthocyanin are the phytochemicals that are naturally found in plants and are

Table 1. Quantitative phytochemical analysis of different flower extracts.

Plant extracts	TPC (mg GAE/g)	TFC (mg RE/g)	TAC (mg c-3-gE/g)
Malus sp.	3.79±0.20	28.69±0.13	4.01±5.22
Chrysanthemum sp.	2.88±0.23	52.19±0.20	6.01±2.67
Matricaria sp.	0.89±0.09	10.84±0.27	4.68±4.06
Lavandula sp.	4.39±0.13	63.46±1.07	22.93±5.19
Rosa sp.	3.89±0.19	13.13±0.93	70.14±4.82
Hibiscus sabdariffa L.	0.89±0.05	11.57±0.89	8.91±1.39
Myosotis sp.	1.77±0.07	15.85±1.65	34.51±18.18
Gomphrena sp.	0.45±0.03	2.56±0.58	3.79±2.04
Jasminum sp.	0.71±0.04	8.68±1.08	2.23±2.78
Lilium sp.	1.29±0.12	8.87±1.03	26.05±2.00

Values are presented as mean ± standard deviation, n = 3. TPC: total phenolic content, TFC: total flavonoid content, TAC: total anthocyanin content.

also known to possess antioxidant, anti-inflammatory, anti-cancer and other pharmacological activities (Tungmunnithum *et al*., 2018). As shown in the result of the current study, the presence of phenolics, flavonoids and anthocyanins was detected in all the flower extracts. Phenolic compounds including phenolic acid and polyphenols are a major class of secondary metabolites existing in most plants and have proven their ability able to delay the ageing process as well as reduce the health risk (Minatel *et al*., 2017). Among 10 selected flower extracts, their total phenolic content (0.45-4.39 mg GAE/g) was found to be much lower than the result shown (8.23-284.8 mg GAE/g) in the study of Zheng *et al*. (2018). The result of the top 3 samples (*Lavandula* sp., *Rosa* sp. and *Malus* sp.) with the highest phenolic content in this study was lower as compared to the extracts (50.8, 39.47-284.8, 8.23-60.58 mg GAE/g, respectively) studied by Zheng *et al*. (2018). Besides, the overall phenolic content in the current study was lesser than the study of Jin *et al*. (2016), which ranged from 1.26 to 24.55 g GAE/100 g dw, but the present result of *Lavandula* sp. (4.39 mg GAE/g) is comparable to the content of *L. angustifolia* Mill. (3.50 g GAE/100 g dw) and *Rosa* spp. were also reported to have a high content of phenolics in the study of Jin *et al*. (2016).

Flavonoids are an important class of secondary metabolites consisting of a large group of polyphenolic compounds and exhibit various health-promoting effects (Kumar and Pandey, 2013). In total, 10 selected flower extracts were found to have rich flavonoid content (2.56-63.46 mg RE/g) and this was higher than the overall content observed (1.18-25.39 mg CAE/g) among the similar samples in the previous study (Zheng *et al*., 2018). Most of the flower extracts possessed higher flavonoid content as compared to the study of Zheng *et al*. (2018), except the *Myosotis* sp. extract. The difference between sample origins, the influence of environmental conditions and extraction methods could lead to the variation in the phytochemical composition of phenolics and flavonoids (Abu Bakar *et al*., 2016; Md Akhir *et al*., 2017).

Anthocyanins are a subclass of flavonoids that are responsible for pigmentation in plants and fruits and have been widely studied for various medicinal purposes (Khoo *et al*., 2017). Most red, blue and purple coloured flowers contain anthocyanins and this could relate to the high content of anthocyanins (2.23-70.14 mg c-3-gE/g) observed among the selected flowers, especially *Rosa* sp., *Myosotis* sp. and *Lilium* sp. extracts with their stronger colouration. The comparison between current and previous studies showed that the anthocyanin content of *Rosa* sp. (70.14 mg c-3-gE/g) was found to be slightly higher than the anthocyanin content of *Rosa indica* (64.52 mg c-3-gE/g) (Vankar and Srivastava, 2010). The environmental factors such as temperature and light as well as the presence of complex compounds including phenols and other constituents could affect the anthocyanin content present in every plant species, resulting in a variety of flower colours (Bolling *et al*., 2010; Mohd Noor *et al*., 2020).

3.2 Xanthine oxidase inhibitory activity of the selected flowers

Table 2 displays the inhibition percentages of the standard, allopurinol as well as the flower extracts and their IC_{50} values. As a result, all flower extracts showed potent xanthine oxidase inhibitory activity, but the inhibition percentages of flower extracts were not in a concentration-dependent manner. The trend is also observed in the study of Wahyuningsih *et al*. (2016) and this could be due to the increasing metabolites along with the sample concentrations that disturb the inhibition of the xanthine oxidase enzyme. In the present study, *Rosa* sp. exhibited the strongest xanthine oxidase inhibitory activity with the IC_{50} value of 0.10 µg/mL, as compared to the other 9 flower extracts including *Hibiscus sabdariffa* L. (0.12 µg/mL), *Malus* sp. (2.59 µg/mL), *Matricaria* sp. (20.89 µg/mL), *Chrysanthemum* sp. (29.04 µg/mL), *Lavandula* sp. (33.33 µg/mL), *Myosotis* sp. (59.81 µg/mL), *Gomphrena* sp. (65.29 µg/mL), *Lilium* sp. (77.27 µg/mL) and *Jasminum* sp. (85.39 µg/mL). Above all, 3 aqueous flower extracts (*Rosa* sp., *H. sabdariffa* L. and *Malus* sp.) displayed stronger xanthine oxidase inhibition ability than the positive control, allopurinol with the IC_{50} value of 4.9 µg/mL.

Xanthine oxidase inhibitors are proven to be effectively used for the treatment of hepatic disease and gout, which is caused by the increased uric acid level and the generation of excessive amounts of superoxide anion radical (Lin *et al*., 2000). *Rosa* sp. could be developed as a xanthine oxidase inhibitor because it showed the most significant xanthine oxidase inhibitory activity with the lowest IC_{50} value in this study. Previous studies stated that rosehip, the fruit of rose plants within the genus *Rosa*, in particular, *Rosa canina* L. exhibited potent biological activity including the anti-inflammatory effect (Jäger *et al*., 2007; Orhan *et al*., 2007). As reported in the literature, the presence of flavonoid and phenolic compounds (catechin and syringic acid), as well as anthocyanins (cyanidin and pelargonidin), was identified in the *Rosa* sp. extracts and these compounds have shown their capabilities to inhibit xanthine oxidase (Kovatcheva-Apostolova *et al*., 2008; Yang and Shin, 2017; Abu Bakar *et al*., 2018; Malik *et al*., 2019).

The xanthine oxidase inhibitory potency of other flower extracts could be taken into consideration for the

Table 2. Percentage of xanthine oxidase inhibition of different flower extracts and the standard, allopurinol.

Samples	Xanthine Oxidase Inhibition (%)					IC_{50} (µg/mL)
	10 µg/mL	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL	
Lavandula sp.	47.11±5.88	35.41±6.45	22.67±4.51	74.02±1.94	83.02±3.73	33.33±8.07
Malus sp.	75.41±17.36	69.33±26.78	50.67±25.54	80.59±15.25	96.26±1.90	2.59±3.8
Jasminum sp.	51.11±22.07	23.56±26.34	42.96±39.23	50.72±3.73	61.86±1.67	85.39±93.06
Matricaria sp.	7.41±5.15	88.59±10.96	73.04±11.30	93.94±3.65	93.54±3.12	20.8±2.77
Rosa sp.	89.04±1.35	66.37±11.89	84.00±18.97	95.14±2.78	93.30±4.00	0.10±0.15
Chrysanthemum sp.	21.19±11.93	38.22±27.84	75.85±15.71	73.35±28.81	89.24±5.15	29.04±5.00
Myosotis sp.	37.48±26.91	52.30±22.19	62.52±21.51	56.63±3.96	59.81±4.57	57.34±40.32
Gomphrena sp.	10.81±9.80	14.67±6.16	11.11±13.56	64.18±4.44	77.27±2.30	65.84±4.84
Lilium sp.	70.37±42.85	75.56±3.56	13.93±24.12	59.52±8.34	65.96±3.36	78.37±13.99
Hibiscus sabdariffa L.	79.41±7.08	78.96±11.70	74.08±7.50	92.39±0.87	91.41±10.09	0.12±0.11
Allopurinol	61.78±0.00	75.11±0.00	82.67±0.00	92.24±0.00	98.11±0.00	4.9±0.00

Values are presented as mean ± standard deviation, n = 3.

gout treatment. In the present study, the aqueous extract of *Chrysanthemum* sp. displayed higher xanthine oxidase inhibitory activity than the result reported by Kong *et al*. (2000), whereas Bustanji *et al*. (2011) reported that the calyx of *H. sabdariffa* L. inhibited 19.4% of xanthine oxidase enzyme activity, which was lower as compared with this study. The previous and current results are varied in terms of the sample localities and the plant part used for analysis. Furthermore, the flavonoid compounds such as luteolin and apigenin isolated from the flower of *Chrysanthemum indicum* were shown to exhibit potent xanthine oxidase inhibitory activity (Cos *et al*., 1998). The major flavonoid, ferulic acid that can be found in *Lavandula angustifolia* was reported to significantly inhibit more than 50 of xanthine oxidase enzyme activity (Spiridon *et al*., 2011; Nile *et al*., 2016).

Hence, the results suggest that all flower extracts are considered as a promising anti-gout agent and the aqueous extracts of *Rosa* sp., *H. sabdariffa* L. and *Malus* sp. with their remarkable xanthine oxidase inhibitory activities should be given priority for further analysis. In addition to the anti-inflammatory and antioxidant activities, the presence of active phytochemicals could act as the natural xanthine oxidase inhibitor and contribute to the anti-gout potential in the flower extracts.

3.3 Correlation between phytochemicals and xanthine oxidase inhibitory activity

From the correlation analysis in the study, the total phenolic content was strongly correlated with xanthine oxidase inhibitory activity, which was about 70%. Meanwhile, positive relationships were observed between the total flavonoid content and total anthocyanin content with the xanthine oxidase inhibitory activity, which were 30% and 40%, respectively. As the result shown in the present study, phytochemical compositions such as phenolics, flavonoids and anthocyanins were positively correlated with the xanthine oxidase inhibitory activity, and the phenolic compounds contributed primarily to the anti-gout activity among the flower extracts. High content of phenolics in *Rosa* sp. extract resulted in its highest xanthine oxidase inhibitory activity and the strong positive correlation was supported by Kılıçgün and Altıner (2010). A similar observation was also found in *Malus* sp. due to its high content of phenolics, contributing to its stronger xanthine oxidase inhibition. Other than phenolics, flavonoids and anthocyanins, the compounds including alkaloids, cardiac glycosides, steroids, tannins and terpenoids are responsible for the xanthine oxidase inhibitory activity (Apaya and Chichioco-Hern, 2011) and this could explain the strong anti-gout potency in *H. sabdariffa* L. extract.

4. Conclusion

This study clearly demonstrated the potential of *Rosa* sp., *H. sabdariffa* L. and *Malus* sp. as an anti-gout agent due to their stronger xanthine oxidase inhibition abilities recorded with lower IC_{50} values and rich content of phytochemicals. The preliminary results of this study could be further investigated through the isolation and identification of active constituents among the flower extracts, toxicity test as well as the *in vivo* experiments for the verification of their abilities in inhibiting the xanthine oxidase enzyme.

Conflict of interest

The authors do not have any conflicts of interest regarding the content of the present work.

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