Edible Flowers

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Edible flowers have been widely consumed for ages until now. The attractive colors and shapes, exotic aroma, and delightful taste make edible flowers very easy to attain. Moreover, they also provide health benefits for consumers due to the unique composition and concentration of antioxidant compounds in the matrices. Knowing the bioactive compounds and their functional properties from edible flowers is necessary to diversify the usage and reach broader consumers.

Keywords: Edible Flowers ; bioactive compounds ; phenolics ; functional properties ; functional food

1. Edible Flowers

The existence of edible flowers has attracted attention in various corners of the world. Since ancient Greece and Rome, edible flowers have been widely used in cooking and are still developing up to date [1][2]. On the basis of Scopus, literature about the edible flower was first published in 1934; then, the number increased dramatically in the last decade. This research topic gained significant attention due to the findings of antioxidant compounds and their functional properties, leading to diversifying the utilization of edible flowers for a number of purposes.

Edible flowers can be applied to a variety of needs as food components. Edible flowers can be consumed directly, pre-cooked or merely used as a garnish because their diverse colors are visually appealing. Nowadays, the use of edible flowers for food and beverages appears to be in demand as the population requires a healthy diet to endorse their immunity in face of a global pandemic. In Indonesia, a typical dish from *Etlingera elatior* (torch ginger) and *Sesbania grandiflora* (turi) flowers is prepared by boiling the flowers and serving them with peanut sauce. Additionally, *Carica papaya* and *Musa sp* flowers are generally consumed as stir-fried vegetables. Several studies reported that roselle (*Hibiscus sabdariffa*) flowers were used in food product development such as jelly, ready-to-drink beverages, carbonated beverages, fermented products, infusion, sauces, and jams [3][4]. The most practical way to consume roselle flowers is by brewing the stock of simplicia with hot water; this infusion is also commonly accompanied by *Clitoria ternatea* (butterfly pea) flower. Another bloom with various colors viz., *Viola sp*. (pansy) is frequently used as garnish for salads, soups, desserts, and beverages [5].

For non-food applications, edible flowers can function as raw materials to produce perfume, natural dye, and cosmetic products. Jasmine flower (Oleaceae family) is predominantly used in the fragrance industry because it contains more than a hundred aromatic compounds [6][7], as well as *Polianthes tuberosa* flower that is also a good source of essential oils [8]. In contrast, pigmented flowers are primarily used for natural dye. The appealing color of torch ginger flowers due to anthocyanin content could be used as a natural dye for lipstick to replace synthetic ones [9], whilst anthocyanins from butterfly pea flowers are utilized as food colorants [10][11]. Unlike torch ginger flowers, which give a pink or red extract color, butterfly pea flowers are commonly found in purple or blue petals, even though there are other colors such as red, white, and pink. Apart from their role in fragrance and natural dye industries, edible flowers are essential in food seasoning, i.e., a variety of roses species [12]. Moreover, edible flowers have become an excellent natural food source because of having various bioactive compounds, such as phenolic acids, flavonoids, and other antioxidant compounds that contribute to health benefits [13][14].

The main bioactive compounds, such as phenolic acids and flavonoids in some edible flowers have specific functional properties. Phenolic acids, including chlorogenic acid, gallic acid, *p*-hydroxybenzoic acid, and *p*-coumaric acid, while flavonoid groups, such as flavones, flavonols, flavanones, and anthocyanins are closely related to antioxidant properties [14][15]. The antioxidant activities of phenolic compounds are reliable in preventing degenerative diseases such as antidiabetic and cardiovascular disease [16]. Edible flowers with a varied composition of phenolic compounds have also been proven as having antimicrobial, anticancer, and anti-inflammatory effects [17][18]. Besides, phenolic compounds are associated with enzyme inhibitory activity. For example, they have inhibitory activity against *α*-glucosidase and *α*-amylase enzymes, which become potential as an effective hypoglycemic agent [19][20]. The phenolics contained by edible flowers also have the capacity to inhibit xanthine oxidase; thus, the uric acid levels in the blood can be controlled [21]. Moreover, phenolic compounds with intense antioxidant activity show neuroprotective effects. Hence, flavonoids can protect the nerve cells of the brain [22].

2. the Functions of Edible Flowers

2.1. Antioxidant Activity

Oxidants are chemical species that usually form as free radicals such as hydroxyl (HO*), alkoxyl (LO*), and reactive oxygen species (ROS) that have unpaired electrons. They are reactive in general and attack other molecules. These chemical species play an essential role in producing energy, synthesizing some essential compounds, and signal transduction. However, they may cause cell damage and lead to some degenerative diseases like cancer, cardiovascular, and neurodegenerative diseases. In an attempt to avoid this cell damage, antioxidants can be applied in scavenging the free radicals. A number of potential sources of natural antioxidants have been identified, including edible flowers.

In flowers, compounds with antioxidant activities are defined as polyphenols, carotenoids, and ascorbic acid [1]. The attractive color of pigment flowers indicates the presence of phenolic acids and flavonoids. It appears in Table 1 that ornamental flowers are containing a higher level of antioxidant compounds than fruit flowers or common horticultural crops [23]. To take advantage of the antioxidant compounds presented in the flowers, some alternatives extraction methods have been developed.

Table 1. Total phenolic content and antioxidant capacity of edible flowers.

Edible Flower	Total Phenolics	DPPH	FRAP	ABTS	Health Benefits	Ref.
Bougenville hybrid	120.7 mg GAE/g	L: 79.62% H: 91.44%	L: 58.80% H: 126.6%	N/A	Analgesic, antidiabetic, anti-inflammatory, antimicrobial, antioxidant, anticancer	[24]
Brassica oleracea	0.57 mg GAE/g	2.71 µmol TE/g	N/A	N/A	Antioxidant, anticancer	[25]
Brassica oleraea var. *italica*	10.27 mg GAE/g	3.85 µmol TE/g	N/A	N/A	Antioxidant, anticancer	[25] [26]
Calendula arvensis	50.26 mg GAE/g	20.9 IC_{50} µg/mL	203.96 mg AAE/g	N/A	Antioxidant, antimicrobial, anticancer	[27]
Calendula officinalis	34.27 mg GAE/g	34.75 mg TE/g	58.96 mg TE/g	48.15 mg TE/g	Antioxidant, anti-inflammatory, antimicrobial	[28]
Carica papaya	0.76 mg GAE/g	64.07%	N/A	N/A	Antioxidant, antibacterial	[29]
Citrus aurantium	87.96 mg GAE/g	87.15 IC_{50} µg/mL	N/A	N/A	Antioxidant, antimicrobial, neuroprotective	[30]
Clitoria ternatea	76.90 mg GAE/g	0.76 IC_{50} µg/mL	10.91 mM TE/g	4.16 mM TE/g	Antioxidant, anticancer, neuroprotective	[31]
Cocos nucifera	222.61 mg GAE/g	40.5 IC_{50} µg/mL	89.84 IC_{50} µg/mL	66.94 IC_{50} µg/mL	Antioxidant, antidiabetic, cytoprotective, hepatoprotective	[32] [33]
Dianthus carmelitarum	12.6 mg GAE/g	1.22 IC_{50} µg/mL	238 mM TE/g	N/A	Antioxidant, antigenotoxic, antimicrobial, anticancer	[34]
Dimocarpus longan Lour.	476.8 mg GAE/g	3.81 IC_{50} µg/mL	N/A	8.8 mM TE/g	Antioxidant, antiinflammatory, antidiabetic	[35] [36]
Etlingera elatior	4.85 mg GAE/g	9.52 IC_{50} µg/mL	19.43 mmol FE/g	N/A	Antioxidant, antimicrobial, neuroprotective	[37]
Hibiscus sabdariffa	29.2 mg GAE/g	78%	2.31 mM TE/g	7.8 mM TE/g	Anti-inflammatory, antioxidant, anticancer	[38] [39] [40]
Moringa oleifera	19.31 mg GAE/g	14.57 IC50 µg/mL	N/A	N/A	Antioxidant, anti-inflammatory	[41]
Musa ABB	9.44 mg GAE/g	27.96 µmol TE/g	20.6 µmol TE/g	30.66 µmol TE/g	Antioxidant, antidiabetic, DF rich source, neuroprotective	[42]
Musa sp. vVar. *elakki bale*	121.8 mg GAE/g	9.35 IC_{50} µg/mL	39.03 mM AA/g	N/A	Antidiabetic, anti-AGEs, antimicrobial	[43] [44]
Nasturtium officinale	1.44 mg GAE/g	7.76 µmol TE/g	N/A	N/A	Antioxidant, anticancer	[25]
Rosa damascena Mill	233.56 mg GAE/g	74.03%	0.64 µg/mL	N/A	Antioxidant	[45]

Edible Flower	Total Phenolics	DPPH	FRAP	ABTS	Health Benefits	Ref.
Tagetes erecta	28.9 mg GAE/g	L: 85.70% H: 94%	L: 60.92% H: 203.8%	N/A	Anti-inflammation, neuroprotective	[24]
Tropaeolum majus	12.95 mg GAE/g	N/A	N/A	9.51 µmol TE/g	Antioxidant	[46]
Viola wittrockiana	44.88 mg GAE/g	26.1 IC_{50} µg/mL	35 mmol Fe/g	N/A	Neuroprotective, antioxidant	[47] [48]

GAE: gallic acid equivalent; L: lowest value detected; H: highest value detected; N/A: not available; TE: trolox equivalent; %: % inhibition; IC50: half maximal inhibitory

Diverse procedures have been proposed to extract antioxidant compounds from edible flowers with different settings of extraction factors, including solvent, time, temperature, and solid-to-solvent ratio. The polar solvents, such as methanol, ethanol, and water have been widely used to extract antioxidant compounds from edible flowers. These solvents are selected for extraction due to the high polarity of phenolic compounds [2]. Additionally, the extractions are commonly taken place at an ambient temperature [49], while some experiments require a higher temperature (35 to 100 °C). The main reason for applying a higher temperature is to reduce the extraction time as the higher the temperature, the shorter the extraction time, and vice versa. Soxhlet is the most frequent extraction method with high temperature, while maceration can be performed in a wide range of operating temperatures [50]. Different extraction procedures could produce varied levels of antioxidant compounds of the resulting extract.

The level of antioxidant compounds is commonly presented as total phenolic contents. However, other antioxidant parameters are evaluated by assays, indicating the antioxidant capacity of edible flowers, such as DPPH (2,2-diphenyl-1-picrylhydrazyl), FRAP (ferric reducing antioxidant power), and ORAC (oxygen radical absorbance capacity) [23]. DPPH is a method for assessing free radical scavenging activity, ferric reducing antioxidant power (FRAP) assesses the ability to reduce free radicals, while ABTS estimates single electron transfer capabilities [51]. Former studies reported that phenolics are the main compounds contributing the antioxidant capacity. Hence, provided that an edible flower has a diverse and greater amount of phenolic compounds, the flower may exhibit high antioxidant activity [52][53]. As a reference, the total phenolic content and antioxidant capacity of some edible flowers assessed by several methods are listed in Table 1.

Table 1 shows the diversity of total phenolic content and antioxidant activity in edible flowers. It is not easy to compare the results of the antioxidant assays nor the reducing activities because different assays are using different reference compounds. Therefore, the results are expressed in different ways in the literature. From these data, it is also challenging to know the differences between a fruit flower or an ornamental flower. Likewise, flowers with intense colors and soft ones. For example, *Musa sp*. Var. Elakki bale and *Citrus aurantium* as fruit flower had phenolic content 121.8 and 87.96 mg GAE/g, respectively. While *Bougenville hybrid* and *Clitoria ternatea* as non-fruit flower had phenolic content 120.7 and 76.9 mg GAE/g. However, flowers with intense color appear to have high total phenolic content such as *Calendula arvensis*, *Viola wittrockiana*, *Hibiscus sabdariffa*, and *Tagetes erecta* at 50.26, 44.88, 29.2, 28.9 mg GAE/g, respectively. Apart from different tests, the authors suspect these differences are also due to differences in the age of the flowers. Because, during senescence, plants will experience biochemical changes and the formation of ROS, which indeed results in a decrease in antioxidant activity [54]. However, this still requires further research.

Phenolic compounds are plant derivative compounds easily found in several vegetables and fruits and also consumed in the daily food intake. For example, kale, cucumber, and celery have total phenolic content (TPC) of 36.89 mg/g, 14.37 mg/g, and 14.95 mg/g, respectively [55][56]. The phenolic content in vegetables is still lower when compared to the phenolic content in edible flowers. The same thing happens in fruit. Mulberry fruit (*Morus atropurpurea* Roxb.) only contains a TPC value of 11.33 mg/g [57]. Moreover, its antioxidant activity is lower than edible flowers. The result of ABTS and DPPH assays were 4.11 and 10.08 µg TE/mL, respectively [57]. Still, there is a wide range of antioxidant levels for edible flowers, fruits, and vegetables. From this study, it can be seen that each type of food matrices has a different antioxidant activity, which is influenced by its antioxidant components.

2.2. Anti-Inflammatory

Inflammation is a physiological response from a host in protecting themselves from toxins and pathogens [58] in the form of infections, chemical exposure, tissue damage, and exposure to bacterial components such as lipopolysaccharide (LPS) [59][60]. Some macrophages, including inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β [61], and inflammatory mediators, such as a nitric oxide (NO) and prostaglandin E2 (PGE2), which is synthesized by inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) [62], if overproduced, can endanger tissues and organisms. Consequences are various inflammation-related diseases, such as rheumatoid arthritis, diabetes, inflammatory bowel disease, atherosclerosis, and cancer [63].

Several studies have shown that flavonoids, anthocyanins, and phenolic acids are active components that are responsible for anti-inflammatory properties, as listed in Table 2 [64]. For example, in the LPS-induced RAW 264.7 system model, anthocyanins from *Hibiscus* (delphinidin 3-sambubioside) can reduce some LPS-induced inflammatory mediators, such as iNOS/NO, interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and TNF-α [65]. In addition, phenolic compounds called ellagic acid from *Rosa rugosa* Thunb flower extract can reduce the production of inflammatory mediators such as NO, PGE2, and inflammatory cytokines such as TNF-α, IL-6, and IL-1β [66]. Other flowers such as *Butea monosperma* and *Ginkgo biloba* L. are also known to inhibit the formation of those inflammatory mediators and cytokines [67][68].

Table 2. Anti-inflammatory activities in edible flowers.

Edible Flower	Compounds	Assessment	Activities	Ref.
Butea monosperma **(Lam.) Taubert**	**Butrin, isobutrin**	**In vivo**	**Suppressed IL-1β, IL-6, IL8, PGE2**	[67]
Ginkgo biloba **L.**	**Bilobetin, isoginkgetin**	**In vivo**	**Suppressed NO, TNF-α, IL-6, PGE2, iNOS, COX-2**	[68]
Hibiscus sabdariffa **L**	**Delphinidin 3-sambubioside, delphinidin**	**In vitro, In vivo**	**Suppressed iNOS, NO, IL-6, MCP-1, TNF-α**	[65]
Moringa oleifera	**Tannins (not specific)**	**In vitro**	**Inhibited protein denaturation in 58%–101%**	[41]
Rosa rugosa **Thunb**	**Ellagic acid**	**In vivo**	**Suppressed NO, PGE2, TNF-α, IL-6, IL-1β, iNOS, COX-2**	[66]
Sesbania grandiflora **L. Fabaceae**	**Flavonoids (not specific)**	**In vivo**	**Inhibited edema formation up to 79% in 5h**	[69]

Another anti-inflammatory activity was also found in M. oleifera flower extract because it prevented protein denaturation and was comparable to standard drug sodium diclofenac [41]. Flavonoids from *Sesbania grandiflora* L. Fabaceae also inhibited edema formation which closely related to inflammation [69]. However, further research is needed to find out which components are really responsible for anti-inflammatory activity and its mechanisms.

2.3. Antimicrobial

Antimicrobial activity in edible flowers depends on the presence of certain microorganism inhibiting compounds. Commonly, those compounds are from the phenolic group. Several antimicrobial activities in edible flowers are listed in Table 3. Phenolic extracts from *Sesbania grandiflora* flower, especially those containing rutin, have inhibitory activity against *Staphylococcus aureus*, *Shigella flexneri*, *Salmonella* Typhi, *Escherichia coli*, and *Vibrio cholera* [70]. Extracts from *Rosa rugosa* flower containing gallic acid also exhibit antimicrobial activity against *Staphylococcus epidermis*, *S. aureus*, *Bacillus subtilis*, *M. luteus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis* [71]. Quinic acid from *Citrus aurantium* L. flower extract also had antimicrobial activity against *Escherichia coli Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus cereus* [72]. *Etlingera elatior* and *Hibiscus sabdariffa* flower also have the inhibition to several pathogen bacteria. Not only phenolic compounds but also proteins can exhibit antimicrobial activity. *Musa sapientum* L. flower contains amino acids called tyrosine and tryptophan that exhibit antimicrobial activity against *S. aureus* and *E. coli* [73]. Based on those facts, it is very possible for edible flowers to become a source of antimicrobial compounds for both the human body and food which functions to keep food from spoiling quickly.

Table 3. Antimicrobial activities in edible flowers.

Edible Flower	Compounds	Method	Microorganisms	Ref
Citrus aurantium **L.**	**Quinic acid**	**Agar well-diffusion**	***E. coli*****,** ***P. aeruginosa*****,** ***S. aureus*****,** ***B. cereus***	[72]
Etlingera elatior	**Gallic acid, caffeic acid, tannic acid**	**Agar well-diffusion**	***S. aureus*****,** ***B. subtilis*****,** ***L. monocytogenes*****,** ***E. coli*****,** ***S. typhimurium*****,** ***P. aeruginosa***	[18]
Hibiscus sabdariffa **L.**	**Phenolics (not specific)**	**Agar cup diffusion**	***Inhibited E. coli*****,** ***S. aureus*****,** ***Str. Mutans*****,** ***P. aeruginosa***	[74]

Edible Flower	Compounds	Method	Microorganisms	Ref
Rosa rugosa	Gallic acid	Micro-broth dilution	*S. epidermidis*, *S. aureus*, *B. subtilis*, *M. luteus*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Proteus mirabilis)*	[71]
Sesbania grandiflora	Rutin	Agar well-diffusion	*S. aureus*, *S. flexneri*, *S. typhi*, *E. coli*, *Vibrio cholera*	[70]

2.4. Anticancer

Cancer is a kind of malignant tumor caused by abnormal cell growth. These cells will develop and spread to other body tissues, referred to as metastasis [75]. Cancer is classified as a deadly disease, and this fact is proven by the high number of new cases and mortality [76]. For example, globally, breast cancer is the most dangerous type of cancer for women. Approximately 1.1 million deaths were reported in 2018. This number is lower than deaths from lung cancer [77][78].

Reactive oxygen species (ROS) is claimed as one of the causes of the development of the cancer phase [79] and involved in tumor cell metastases [80]. According to [69], an approach with antioxidants can reduce cell injury or inflammation caused by ROS, including superoxide (O^{2-}), hydroxyl radical (OH), and H_2O_2. Therefore, antioxidants have a major effect as antimetastatic and chemopreventive [80].

Recent studies reveal the relationship between antioxidant activity and cancer inhibitory [81]. Antioxidant compounds, including polyphenols, phenolic acids, flavonoids, and their derivatives, have an important role in disrupting the development of cancer cells [79][82], vis., initiation, promotion, and progression stages and also polyphenols are referred to as anti-carcinogenic agents [83]. The most common approach to cancer treatment is chemotherapy. This therapy relies on the ability of strong chemical medicine to destroy, slow down, and even stop the growth of cancer cells. However, this treatment provides side effects for patients, so the use of natural medicine is proposed as an alternative treatment [75].

Natural or herbal medicine is an alternative treatment that uses natural ingredients such as plants, including edible flowers. Several studies revealed that bioactive compounds such as phenolic and flavonoids from edible flowers have anticancer activity. In addition, previous studies reported that phenolic compounds from edible flowers have preventive and healing properties [17]. Polyphenols from plants have strong antioxidant activity and can provide a protective effect, especially against DNA damage (oxidative damage). Oxidative damage is the beginning of cancer development or also known as a crucial stage. Some common phenolics such as chlorogenic acid, quercetin, gallic acid, caffeic acid, and tannic acid are against cancer activity [18][60][62].

In Table 4, we have listed several edible flowers that have been shown to inhibit some cancer cells. MTT (dimethylthiazol-diphenyltetrazolium bromide) colometric assay and SRB (sulforhodamine B) assay were used. MTT assay determines cell viability, while SRB assay is a test for chemosensitivity [84]. Based on in vitro tests using MTT and SRB assays, these flowers have the ability to inhibit the growth of breast, cervical, hepatocellular, lung, and colon cancer cell line. However, there is still very limited research that shows how long the dose of edible flower should be given to patients with cancer until the cancer cells are completely removed from the body.

Table 4. Anticancer activities in edible flowers.

Edible Flower	Compounds	Assessment	Cancer Lines	Ref.
Calendula officinalis	Chlorogenic acid, quercetin, isorhamnetin	In vitro (MTT assay)	Breast cancer cell line (MCF-7, MDA-MB-231, Hs578T)	[85]
Carica papaya	Stigmast-4-ene-3-one, benzyl β-D-glucopyranoside, uracil	In vitro (SRB assay)	Breast cancer cell line (MCF-7), cervical cancer (HeLa), hepatocellular (Hep-G2), lung carcinoma (NCI-H460)	[86]
Etlingera elatior	Gallic acid, caffeic acid, tannic acid	In vitro (MTT assay)	Human breast carcinoma cell lines (MCF-7 and MDA-MB-231), hepatocellular carcinoma (HepG2), colon carcinoma (HT-29), cervical cancer (HeLa)	[18] [87]
Musa paradisiaca	Phenolics (not specific)	In vitro (MTT assay)	Cervical cancer cell line (HeLa)	[88]
Sesbania grandiflora L. Fabaceae	Flavonoids (not specific)	In vitro (MTT assay)	Human cancer cell line (HeLa)	[69]

2.5. Neuroprotective Agent

Neurodegenerative disorders (ND) are a progressive loss of central nervous system (CNS) or neuron dysfunction such as Alzheimer's, Parkinson's, and Huntington's diseases caused by cell degeneration and even cell death [89][90]. This neuron degeneration is a polyfactorial or multifactorial genetic disease that involves a combination of genetic (e.g., genetic mutase) and non-genetic or environmental factors such as oxidative stress, inflammation, neuronal apoptosis, etc. [89][91].

Alzheimer's disease (AD) is a brain disorder that results in decreased memory, cognitive decline, and behavior change gradually. This condition is more commonly occur in people over 65 years old. The initial stage of this disease affects the ability of memory, while sensory and motor functions are still normal. Whilst Parkinson's disease (PD) is a neurological disease that affects movement coordination. As a result, sufferers have difficulty regulating body movements such as walking, regulating balance, rigidity, tremor, and bradykinesia (slowness of movement) [92].

Reduction of acetylcholine (ACh) levels in presynaptic is a symptom of cognitive impairment in AD's sufferers. Acetylcholine is a neurotransmitter that sends signals from one nerve cell to the target. The increase in acetylcholine can be done by inhibiting the activity of the enzyme cholinesterase or acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) in hydrolyzing acetylcholine [17][93]. While ROS is claimed to be involved in the selective degeneration of dopaminergic neurons in PD sufferers. This mechanism occurs in the metabolism of dopamine (as a neurotransmitter), which produces free radicals that cause oxidative stress [92].

Neuroprotective agents are needed as an approach in protecting neuron damage to the CNS. Parts of medicinal plants such as leaves, flowers, fruits, and seeds are reported to be used as alternative therapies [92]. Edible flowers are high in phenolic compounds that can act as a neuroprotective agent. Phenolics such as flavonoids provide the effect of increasing the function or regeneration of nerve cells, avoiding the formation of ROS, and reducing the oxidation of proteins. Furthermore, flavonoids have various benefits in protecting the nerves of the brain, including minimizing nerve inflammation and nerve injury caused by neurotoxins, as well as improving cognitive function and memory [22][91]. Non-flavonoid phenolics such as phenolic acids also have a similar ability [17].

From Table 5, it can be seen that some of the neuroprotective mechanisms of edible flowers are inhibiting the performance of the enzymes. Phenolic acid, such as syringic acid, salicylic acid, chlorogenic acid from *Butea monosperma* and *Sesbania grandiflora* inhibit the enzymes AChE and BuChE which leads to prevent the breakdown of acetylcholine, so that the acetylcholine content in the nerves does not decrease [17]. *Viola wittrockiana* flower is also known to inhibit AChE and monoamine oxidase A [48]. This inhibitory activity may be due to the high content of quercetin and other flavonoids such as anthocyanin. Quercetin also inhibits the secretase enzyme in producing Amyloid-β (Aβ) [94] [95]. Aβ is a peptide that has been associated with Alzheimer's due to the accumulation of amyloid plaque. Another mechanism was also found in *Crocus sativus* L. Based on in vivo test results, the content of crocins can reduce extracellular ATP in the retina, so that retinal nerve damage can be avoided (Maggi2020).

Table 5. Neuroprotective activities in edible flowers.

Edible Flower	Compounds	Assessment	Activities	Ref.
***Butea monosperma* (Lam.) Taub.**	**Syringic and salicylic acid**	**In vitro enzyme inhibitory**	**Inhibited AChE and BuChE**	**[17]**
***Crocus sativus* L.**	**Crocins**	**In vivo (morphological evaluation by quantitative histology)**	**Protect retinal neurons from light damage**	**[96]**
***Sesbania grandiflora* L.**	**Chlorogenic acid, neochlorogenic acids and catechin hydrate**	**In vitro enzyme inhibitory**	**Inhibited AChE and BuChE**	**[17]**
Viola x wittrockiana	**quercetin-3-O-(6-O-rhamnosylglucoside)-7-O-rhamnoside**	**In vitro enzyme inhibitory**	**Inhibited AChE and monoamine oxidase A**	**[48]**

In addition, when compared with other matrices such as fruit, flowers such as marigold (*Tagetes erecta*) [60] and *E*. *elatior* [18] showed higher chlorogenic acid content when compared to Mulberries fruit extract (0.136–0.517 mg / g) [32]. This information indicates the high potential of edible flowers to be a neuroprotective agent. However, more data are needed to draw this conclusion.

2.6. Antidiabetic

Diabetes mellitus (DM) is a non-communicable disease characterized by an abnormally elevated blood glucose level. This condition due to pancreatic beta cells damage so that insulin production has decreased or not fulfilled, called type I diabetes mellitus (T1DM). Meanwhile, type II diabetes mellitus (T2DM) is normal insulin production but the body is less sensitive, also called insulin resistance [97][98].

Insulin is a hormone produced by pancreatic beta cells. This hormone functions to control blood sugar by converting glucose into energy and spread throughout the body or stored in the form of glycogen. Failure of insulin production can cause an accumulation of glucose in the blood, also called hyperglycemia. Insulin therapy is used as a general approach for people with type I diabetes. While T2DM is non-insulin-dependent [20]. Furthermore, other therapeutic approaches that can be taken are by inhibiting the action of the α-glucosidase and α-amylase enzymes because α-amylase is a starch hydrolyzing enzyme, while α-glucosidase plays a role in the absorption of glucose in the small intestine. The purpose of the inhibition of digestive enzymes is to suppress the increase in blood glucose by delaying the digestion of carbohydrates [20][99]. Then, besides maintaining blood sugar, the most important goal of diabetes treatment is to prevent or delay complications, such as microvascular complications, including damage to the eye (retinopathy), kidney dysfunction (nephropathy), nerves dysfunction (neuropathy), diabetic angiopathy (narrowing of the blood vessels), and macrovascular complications, including cardiovascular disease [100][101].

Acarbose [98] and metformin are antidiabetic drugs that are widely consumed by people with type 2 diabetes. This drug is quite expensive and has undesirable side effects [102]. At present, natural products are being highlighted as an alternative treatment for managing diabetes. Medicinal plants have the potential as safe and effective hypoglycemic agents (lowering blood sugar level). This effect is associated with the presence of natural bioactive compounds such as flavonoids [97]. Phenolic compounds are also reported as natural antioxidants that can repair oxidative damage and has inhibitory activity against α-glucosidase and α-amylase enzymes [19][20]. It also has been reported [103] the involvement of several phenolic constitutions such as kaempferol, quercetin 3-rutinoside, and quercetin 3-rhamnoside (quercetin) in carbohydrate metabolism, reducing insulin resistance, dyslipidemia, and hyperglycemia. Insulin secretion in diabetic rats can be increased by p-coumaric acid. Moreover, elevated liver and muscle glycogen levels show better insulin activity in streptozotocin-induced diabetic rats [103][104].

In flowers, several antidiabetic activities has been found and listed in Table 6. The phenolic components of the *D*. *volubilis* flower extract are reported to provide hypoglycemic effects and therapeutic benefits. This is related to the results of the enzyme activity test involved in the digestion process, namely the IC50 value of *D*. *volubilis* were 2780.09 ± 21.19 µg/mL in inhibiting α-glucosidase and 360.68 ± 1.26 µg/mL in α-amylase [20]. Rutin compound in *Dianthus calocephalus* Boiss provides high inhibitory activity on α-glucosidase [105].

Table 6. Antidiabetic activities in edible flowers.

Edible Flower	Compounds	Assessment	Activities	Ref.
***Chrysanthemum morifolium* Ramat**	**Chlorogenic acid and luteolin**	**In vivo**	**Reduced blood glucose level, inhibited MCP-1 production**	**[106]**
***Dianthus calocephalus* Boiss**	**Rutin**	**In vitro enzymes inhibitory**	**Inhibited α-glucosidase**	**[105]**
Dregea volubilis	**Gallic acid, ferulic acid, rutin, ellagic acid, quercetin, cinnamic acid**	**In vitro enzymes inhibitory**	**Inhibited α-glucosidase and α-amylase**	**[20]**
***Musa sp*. Var. elakki bale**	**Phenolics (not specific)**	**In vivo**	**Inhibited AGEs formation**	**[44]**

Not only doe edible flowers inhibit α-glucosidase and α-amylase, but they can also inhibit the formation of certain compounds. Evaluation of administration of flower extracts in obese diabetic mice was carried out. Animal models were given the AIN-93 M diet containing 1% and 5% of *Chrysanthemum morifolium* (CM) flower extracts for 5 weeks. The result showed that CM flower extract inhibited the production of MCP-1 (monocyte chemoattractant protein-1). MCP-1 plays an important role in inflammation, which produces tissue with insulin resistance [106]. *Musa sp*. var. Elakki bale is also reported to inhibit the formation of AGEs (advanced glycation end-products). The accumulation of AGEs can cause complications in diabetics, for example, kidney failure [43].

2.7. Uricosuric Agent

Uricosuric such as benzbromarone and probenecid are a class of drugs commonly used for the treatment of hyperuricemia. This condition is characterized by increased uric acid production, decreased excretion by the kidneys, or a combination of both, which causes high levels of uric acid in the blood [107][108]. High uric acid production and poor

excretion system can cause the accumulation of uric acid crystals (monosodium urate). This occurs in the joints so that it can be at risk for arthritis Gout. Not only that, other risk factors such as hypertension, atherosclerosis, diabetes are also reported as a result of high uric acid levels [109][110].

Uric acid is an organic compound produced through purine metabolic pathways [108]. There are two sources of purines, namely purines that are naturally produced by the body (endogenous) such as liver, intestine, other tissues like kidneys, muscles, and vascular endothelium, and then exogenous purines derived from food intake such as plant or animal foods [111][112].

The formation of uric acid involves xanthine oxidase (XO) enzyme, adenine, and guanine. First, adenosine monophosphate (AMP) is converted to inosine (as an intermediate product) through the process of deamination and dephosphorylation by nucleotidase, then guanine monophosphate (GMP) is converted to guanosine by nucleotidase. Nucleoside phosphorylase (PNP) will convert inosine and guanosine to hypoxanthine and guanine. Furthermore, hypoxanthine is converted to xanthine by XO, while guanine becomes xanthine through a deamination process. Finally, uric acid is formed from xanthine due to xanthine oxidase oxidation [112]. AMP and GMP are purine nucleotides that contain bases hypoxanthine.

Treatments that can be done to control uric acid levels in the blood include suppressing production by inhibiting the action of the XO enzyme, regulating reabsorption and secretion in the kidneys. Allopurinol and febuxostat are XO inhibitors that are reported as a common approach to hyperuricemia [21]. Several studies have reported that treatment with XO inhibitors not only beneficial effects on the kidneys but also edematous brain, coronary ischemia, liver disorders, atherosclerosis and can improve endothelial function [113]. Unfortunately, people with allopurinol hypersensitivity can experience a skin rash, toxic epidermal necrolysis, erythematous rash, fever, hepatitis, and acute renal failure during allopurinol consumption. Moreover, it also can induce hepatotoxicity related to benzbromarone, so the idea of anti-hyperuricemia therapy that is safe and can minimize side effects is needed [21][114].

Several studies have reported that the involvement of phenolic compounds in the inhibition of xanthine oxidase (XO) and given that phenolic is a good bioactive source. [109] conducted a study of several phenolic compounds that were associated with enzyme inhibitory activity. The results showed that phenolic compounds such as ferulic, gallic and caffeic acid have the potential to inhibit XO. It also provides anti-inflammatory activity. In addition, in silico drug and SAR (structure-activity relationship) tests were carried out to qualify whether the compound could be used as a drug candidate or not. The results showed that the compound of ferulic, gallic, caffeic, and sinapic acid had good drug scores, confirmed to be safe for intake and non-mutagenic.

In flowers, the beneficial effects on the prevention or healing of hyperuricemia may still be minimal (listed in Table 7). *Chrysanthemum sinense*, which contains luteolin, diosmetin, apigenin, caffeic acid, etc., is very good at inhibiting XO enzyme after being tested in vitro [115]. Even in the in vivo test, *Chrysanthemum indicum* Linne, which contains coumarin, trans-cinnamic acid, etc., can reduce serum uric acid levels [116]. Moreover, the flavonoids in *Hibiscus sabdariffa* L. are also able to reduce uric acid levels in the body by providing a diuretic effect [117]. However, seeing the results shown above, it may be that phenolic compounds from various edible flowers also have potential as uricosuric agents, and this needs further research.

Table 7. Uricosuric activities in edible flowers.

Edible Flower	Compounds	Assessment	Activities	Ref.
***Chrysanthemum indicum* Linné**	**Coumarin, trans-cinnamic acid**	**In vivo**	**Lowering serum uric acid levels**	**[115]**
Chrysanthemum sinense	**Luteolin, diosmetin, apigenin, caffeic acid**	**In vitro enzyme inhibitory**	**Inhibition XO enzyme**	**[116]**
***Hibiscus sabdariffa* L.**	**delphinidin-3-O-sambubioside, cyanidin-3-O-sambubioside, quercetin, rutin, chlorogenic acid**	**In vivo**	**Diuretic effect**	**[64]**

2.8. Anti-Hemolytic

Hemolysis is the release of hemoglobin into the surrounding environment due to the rupture of the erythrocyte membrane of red blood cells (RBC). Hemolysis can occur in vivo and in vitro. Hemolysis in vivo includes autoimmune hemolytic anemia, transfusion reactions, paroxysmal nocturnal hemoglobinuria (blood disorders due to genetic mutase), paroxysmal cold hemoglobinuria, infections, and in vitro, such as blood sampling, processing, or improper removal of specimens [118][119].

Some cases, for example hypotonic hemolysis is an extreme condition in human erythrocytes caused by low extracellular osmotic pressure. To achieve balance, erythrocytes will absorb water from the extracellular medium. However, when excessed, causes swelling and cell rupture. Another case, erythrocyte membranes consist of polyunsaturated fatty acids that are susceptible to lipid peroxidation reactions. Peroxidation reactions can be mediated by the presence of free radicals that will form peroxyl radicals. Peroxidation of membrane lipids is a free-radical chain reaction, triggering the erythrocyte membrane to be quickly damaged and leading to hemolysis [120][121].

The phenolic content is known as a natural antioxidant that can provide a protective effect toward cell damage by acting as a reducing agent, hydrogen donators, free radical scavengers, and singlet oxygen quenchers [120][122]. Several substances such as butadiene, rutin, and flavonoids can stabilize erythrocyte membranes that undergo hypotonic hemolysis. It is also associated with the anti-inflammatory activity of triterpene compounds against cell membranes [123][124][125].

Table 8 compiles the antihemolytic activities in several edible flowers. *Clitoria ternatea*, known as butterfly pea flowers, had reported having some effects on hemolysis in erythrocytes with type O^+ blood [126]. The results showed that the concentration of 40–120 µg/mL extract had a protective effect against hemolysis. Concentrations of 120 µg/mL extract provide almost 50% of the effect on reducing hemolysis. This can be attributed to the involvement of components contained in flower extracts, including gallic, syringic, 2-hydroxycinnamic, protocatechuic, 2,4 dihydroxybenzoic, *p*-coumaric, caffeic, ferulic, and ellagic acids, also several compounds from the flavonoid group such as quercetin-3-rutinoside; procyanidin A2; epicatechin; and delphinidin-3-O-glucoside. *Prunus avium* that contains hydroxycinnamic acid, 5-O-caffeoylquinic acid, p-coumaric, quercetin, and kaempferol also inhibited hemoglobin oxidation [127].

Table 8. Antihemolytic activities in edible flowers.

Edible Flower	Compounds	Assessment	Activities	Ref.
***Clitoria ternatea* L.**	**2,4-Dihydroxybenzoic acid, protocatechuic acid, caffeic acid, *p*-coumaric acid, procyanidin A2, delphinidin-3-O-glucoside, ellagic acid**	**In vitro**	**Reduction of hemolysis by altering lipid packaging and protecting against oxidative damage**	**[126]**
Prunus avium	**Hydroxycinnamic acid, 5-O-caffeoylquinic acid, p-coumaric, quercetin, kaempferol**	**In vitro**	**Inhibition hemoglobin oxidation**	**[127]**
Thymus satureioides	**Caffeic acid, rosmarinic acid, luteolin 7-glycoside, hesperetin**	**In vitro**	**Protect and stabilize erythrocyte membrane from lesions**	**[128]**

Anti-hemolytic assay can be done using 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) as an initiator of peroxyl radicals that produce free radicals to induce erythrocyte damage. The aqueous extract of *Thymus satureioides* showed good activity against AAPH. They ameliorate the half time of hemolysis in rabbit blood [128].

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