Review Article

*Citrus maxima* (Brum.) Merr. (Rutaceae): Bioactive Chemical Constituents and Pharmacological Activities

Biswash Sapkota,¹ Hari Prasad Devkota,² and Prakash Poudel³

¹Department of Pharmacy, Madan Bhandari Academy of Health Sciences, Hetauda 44100, Nepal
²Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honnachi, Chuo-ku, Kumamoto 862-0973, Japan
³Pharmacy Program, Gandaki University, Pokhara 33700, Nepal

Correspondence should be addressed to Prakash Poudel; poudelprakash@gmail.com

Received 16 August 2021; Revised 26 February 2022; Accepted 5 May 2022; Published 30 May 2022

Academic Editor: Marinella De Leo

Copyright © 2022 Biswash Sapkota et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Citrus maxima* (Burm.) Merr. (family Rutaceae), commonly known as Pomelo, is an ethnomedicinally, pharmacologically, and phytochemically valued species. Various ethnomedicinal reports have revealed the use of *C. maxima* for cough, fever, asthma, diarrhea, ulcer, and diabetes and as a sedative. Numerous phytochemicals have been reported from *C. maxima* such as polyphenols, terpenoids, sterols, carotenoids, vitamins, and amino acids. The plant possesses significant bioactivities like antioxidant, antimicrobial, anti-inflammatory, analgesic, anticancer, antidiabetic, anti-Alzheimer’s disease, insecticidal, anxiolytic, hepatoprotective, antimalarial, and antiobesity. Extensive research is necessary to explore the detailed mechanism of action of extracts and compounds to design effective medicines, herbal products, and functional foods.

1. Introduction

*Citrus maxima* (Burm.) Merr. (syn. *Citrus grandis* (L.) Osbeck) (Figure 1) belongs to the family Rutaceae. It is a perennial tree commonly known as Pomelo, Bhogate, Shaddock, Papanus, Pummelo, etc. in various parts of the world, as shown in Table 1. The plant is indigenous to Asia and is commercially grown in China, Nepal, Thailand, Malaysia, India, Vietnam, Indonesia, Philippines, Japan, and many other Asian countries. Lately, it has been introduced to many tropical nations [1–3]. It grows widely in temperates 25–32°C and rainfall 1,500–2,500 mm within a 3-4 months dry season. It raises well in rough sand to heavy clay but favors fertile soils [2, 3]. Figure 1 shows various plant parts of *C. maxima*, which include the whole plant, whole fruit, albedo, and pulp. It has big round-shaped edible fruits with pink or white flesh. It is traditionally used for ulcers, febrifuge, dyspepsia, lumbago, fever, cardiotonic, gastrointestinal disorders, diabetes, and cardiovascular disease [4–9]. Various chemical constituents are reported from many parts of the *C. maxima* plant. The extracts or pure compounds from this plant have also been evaluated for a wide range of biological activities. The aim of this review article is to provide comprehensive outline of phytochemistry and pharmacological aspects of the plant and to attract scientific communities for further studies on possible utilization of *C. maxima* in the field of pharmaceutical, nutraceutical, and cosmeceutical industry.

2. Methodology

Scientific information about ethnomedicinal uses, phytoconstituents, and in vivo and in vitro biological activities of different parts of *C. maxima* was collected from published articles retrieved through several relevant databases including Google Scholar, PubMed, Chemical Abstract, Scifinder, Web of Science, and Scopus. The database was searched with the keywords such as *Citrus maxima*, pummelo, and *Citrus grandis* along with pharmacological activity, phytochemicals, ethnomedicinal uses, toxicity, etc.
3. Traditional Uses

It is well documented for its ethnomedicinal values in many countries [4, 5, 10, 11]. Fruits are used as stomach tonic, appetizer, cardiac stimulants and for the treatment of inflammation, cough, asthma, obesity, leprosy, mental aberration, epilepsy, headache, diarrhea [12–15], antipyretic, and antiemetics agents [16]. Pulp has been used traditionally for cosmetic purpose. The seeds are used against lumbago, dyspepsia, and coughs. Leaves are used for the treatment of epilepsy, cholera, and convulsive cough while decoction is useful on swellings and ulcers [17–19]. The details of traditional use of the plant are given in Table 2.

4. Bioactive Chemical Constituents

Phytochemicals belonging to different chemical classes such as alkaloids, saponins, carbohydrates, phenols, flavonoids, glycosides, anthraquinone, amino acids, carotenoids, and terpenoids are present [29–32]. Table 3 shows the details of phytoconstituents present, their classes, and plant parts used for isolation.

4.1. Alkaloids. Alkaloids have been isolated from most of the parts including stem, flower, fruit, peel, root, and bark of the plant. The structures of the isolated alkaloids are shown in Figure 2. Some of the isolated acridone alkaloids are citpressine-I and II, 5-hydroxynoracronycine, buntamine, citracridone-I, II, and III [35], citrusinine-I, grandisine-I and II, glycocitine-I, natsucitrine-II, and prenylcitpressine [33, 34]. Alkaloids like buntanbismine, buntanmine A, afoline, baiyumine-A and -B, caffeine, citbismine-A, -B, and -C, citropone-A and -B, geibalsine, honyumine, pumiline, p-synephrine, theobromine, theophylline, and paraxanthine are also reported from the plant [28, 35, 37–39, 41, 43, 49].

---

Table 1: Some common names of Citrus maxima.

| Language  | Common name                      |
|-----------|----------------------------------|
| Nepali    | Bhogate                          |
| English   | Pummelo, shaddock, pumelo        |
| Sanskrit  | Madhukarkati                     |
| Italian   | Pomelo                           |
| French    | Pamplemousse                     |
| Portuguese| Jamboa                           |
| Spanish   | Pamelmusa                        |
| Polish    | Pompea                           |
| Indonesian| Jeruk Besar, Jerukbali           |

Figure 1: Photographs of tree (a), ripe fruits (b), fruit (c), fruit internal section (d), the flesh (e), and seeds (f) of C. maxima.
4.2. Benzenoids. Benzenoids are the major volatile phytochemicals that are essential for attracting insects for pollination [70]. Some of the isolated benzenoids (Figure 3) are crenulatin, diphenylamine, methyl N-methyl anthranilate, and p-hydroquinone [34].

4.3. Coumarins. Different coumarins isolated from C. maxima are 5-methoxyseselin [49], 5-[(6′,7′-dihydroxy-3′,7′-dimethyl-2-octenyl)oxy]psoralen, 5-[(7′,8′-dihydroxy-3′,8′-dimethyl-2-nonadienyl)oxy]psoralen [50], 5-geranyloxy-7-methoxy-coumarin [21], 5-demethyltoddannol, umbelliferone [33], 8-(3-hydroxy-2,2-dimethylpropyl)-7-methoxy-2H-chromen-2-one, auraptene, buntansin, citric acid, decylacetate, fumaric acid, hexanal, malonic acid, cinnamic acid, and vanillic acid [59, 66].

4.4. Carotenoids. Carotenoids are important dietary constituents and also improve the immune response in the plant [71]. The isolated carotenoids from the fruit include β-carotene, phytoene, lutein, zeaxanthin, α-carotene, β-cryptoxanthin, and lycopene [45–48, 72].

4.5. Flavonoids. Flavonoids are one of the most reported chemical classes from this plant (Table 3). Apart from hesperidin, naringenin, and neohesperin, which are common in citrus plants, flavonoids like acacetin, apigenin, cosmosin, diosmetin, diosmin, eriocitrin, hesperidin, honycitrin, luteolin, isosinensetin along with polymethoxyflavones like 5,6,7,8,4′-(tangeritin or ponkanetin), 5,6,7,8,3′,4′-pentamethoxy-(nobiletin), and 5,7,4′-trimethoxy-(apigenin trimethyl ether) are also reported [62–65, 67]. Structures of some of the main flavonoids are shown in Figure 5.

4.6. Phenolics. Phenolics are essential phytochemicals against stress in plants [73]. Some of the isolated phenolic compounds (Figure 6) from its fruit are caffeic acid, 4-hydroxy-3-methoxy cinnamic acid, 4-hydroxycinnamic acid, gallic acid, and vanillic acid [59, 66].

4.7. Steroids. Some steroids including β-sitosterol, campesterol, daucosterol, and stigmasterol are reported from the peel, root, and fruit of this plant [21, 65, 68].

4.8. Terpenoids. C. maxima is also enriched with terpenoids. Tritterpenoids like limonin, deacetylomelin, nomilin glucoside, deoxyxlinomin, obacunone glucosides, obacunone, and nomilinc acid are the major terpenoids (Figure 7) [28].

4.9. Carbohydrates and Amino Acids. Fructose, glucose, pectin, and sucrose are the different carbohydrates found in fruit, peel, and C. maxima leaves [29, 30]. Similarly, amino acids like aspartic acid, proline, alanine, glycine, serine, arginine, asparagine, lysine, glutamic acid, isoleucine, leucine, tryptophan were also isolated from C. maxima [29, 74].

4.10. Essential Oil Constituents. Essential oils are also recorded from its leaves, flower, and peel which includes (Z)-ocimene, 4-methyl-1-hexene, 3,3-dimethyl-1-hexene, geraniol, [75–77] geranyl acetate, limonene, geranyl formate, linalool, nerol, nerolidol, sabinen, α, β -pinene, β-farnesene, and β-myrcene [53, 55, 78].

4.11. Miscellaneous Compounds. In addition to the compounds mentioned above, a few compounds like L-ascorbic acid, citric acid, decyl acetate, fumaric acid, hexanal, malonic acid, succinic acid, α-tocopherol, pentadecanoic acid, hexadecanoic acid, tetradecanoic acid have been isolated from fruit juice, peel, and leaves of C. maxima [28, 79].
Table 3: Details of phytochemicals present in *Citrus maxima*.

| Class     | Compounds name     | Plant parts used                  | References |
|-----------|-------------------|-----------------------------------|------------|
|           | 5-Hydroxynoracronycin | Stem bark                          | [33]       |
|           | Buntanine          | Root bark                          | [34]       |
|           | Citpressine-I, II  | Stem bark and root bark            | [33, 34]  |
|           | Citracridone-I, II | Stem bark and root bark            | [33, 34]  |
|           | Citricidine-III    | Stem bark                          | [35]       |
|           | Citrusinine-I      | Stem bark                          | [33]       |
|           | Glycocitrine-I     | Stem bark                          | [35]       |
|           | Grandisine-I and II| Stem bark                          | [35]       |
|           | Grandisine         | Stem bark                          | [33]       |
|           | Natsucitrine-II    | Stem bark                          | [35]       |
|           | Prelychrisine      | Stem bark                          | [33]       |
|           | Atalafoline        | Stem bark                          | [28]       |
| Acridone alkaloids | Baijumines A, B   | Root bark                          | [36]       |
|           | Buntambismin       | Stem bark                          | [37]       |
|           | Buntanamine-A      | Stem bark                          | [33]       |
|           | Caffeine           | Flower                             | [38]       |
|           | Citbismines A, B, C| Root                               | [39]       |
|           | Citropone-A and -B | Root bark                          | [40]       |
|           | Geibalansine       | Stem bark                          | [28, 41]  |
|           | Honyumine          | Root bark                          | [42]       |
|           | Pumiline           | Root                               | [4]        |
|           | p-Synephrine       | Fruits and leaves                  | [43]       |
|           | Theobromine        | Flower                             | [38]       |
|           | Theophylline       | Flower                             | [38]       |
|           | Paraxanthanine     | Flowers                            | [38]       |
| Benzenoids | Diphenylamine      | Root bark, stem bark, fruit juice  | [34]       |
|           | Methyl N-methylantranilate | Leaves                      | [44]       |
|           | Phytone            | Fruits                             | [45–47]   |
|           | α-carotene         | Fruits                             | [45–47]   |
|           | β-carotene         | Fruits                             | [45–47]   |
| Carotenoids | β-cryptoxanthin    | Fruits                             | [45–47]   |
|           | Lutein             | Fruits                             | [48]       |
|           | Zeaxanthin         | Fruits                             | [48]       |
|           | Lycopene           | Fruits                             | [48]       |
|           | 5-Methoxyseselin   | Root bark                          | [49]       |
|           | 5-[(6',7'-Dihydroxy-3',7'-dimethyl-2-octenyl)oxy]psoralen | Fruit peel                    | [50]       |
|           | 5-[(7',8'-Dihydroxy-3',8'-dimethyl-2-nonadienyl)oxy]psoralen | Fruit peel                    | [50]       |
|           | 5-Geranoxy-7-methoxy-coumarin | Root and stem bark        | [21]       |
|           | 5-Demethyltoddannol| Stem bark                          | [33]       |
|           | Umbelliferone      | Stem bark                          | [33]       |
|           | 8-(3-Hydroxy-2,2-dimethylpropyl)-7-methoxy-2H-chromen-2-one | Fruit peel                    | [50]       |
|           | Auraptene          | Peel                               | [50]       |
|           | Bergamottin        | Peel                               | [33]       |
|           | Buntansin          | Stem bark                          | [33]       |
|           | Citrubentin        | Stem bark                          | [33]       |
| Coumarins | Columbianosides I, II | Fruit pericarp                  | [51]       |
|           | Crenulatin         | Stem bark                          | [33]       |
|           | Epoxybergamottin   | Peel                               | [50]       |
|           | Honyumedin        | Stem bark                          | [34]       |
|           | Marmin            | Peel                               | [50]       |
|           | Meranzin hydrate I, II, III, IV | Fruit pericarp              | [51]       |
|           | Paniculin III      | Fruit pericarp                     | [51]       |
|           | Scoptelin          | Stem bark                          | [33]       |
|           | Suberenone         | Stem bark                          | [33]       |
|           | Suberosin          | Stem bark                          | [33]       |
|           | Ulopteron          | Stem bark                          | [33]       |
|           | Umbelliferone      | Fruit flesh, stem bark             | [33, 52]  |
|           | Xanthohydrate      | Stem bark                          | [33]       |
|           | Xanthylatin        | Stem bark                          | [33]       |
| Class                  | Compounds name                  | Plant parts used                  | References |
|-----------------------|---------------------------------|-----------------------------------|------------|
| Constituents in essential oil (volatile constituents) | (Z)-Ocimene                      | Flower, peel, leaves              | [53]       |
|                       | 4-Methyl-1-hexene               | Flower, peel, leaves              | [54]       |
|                       | 3,3-Dimethyl-1-hexene           | Flower, peel, leaves              | [54]       |
|                       | Geraniol                        | Flower, leaves                    | [53, 56]   |
|                       | Geranyl formate                 | Flower, peel, leaves              | [54]       |
|                       | Geranyl acetate                 | Flower, peel, leaves              | [54]       |
|                       | Limonene                        | Flower, peel, leaves              | [53]       |
|                       | Linalool                        | Flower, peel, leaves              | [53]       |
|                       | Nerol                           | Fruit peel                        | [57]       |
|                       | Nerolidol                       | Fruit peel                        | [53, 55]   |
|                       | Sabinene                        | Fruit peel                        | [53, 55]   |
|                       | α,β-Pinene                      | Flower, peel, leaves              | [53–55]    |
|                       | β-Farnesene                     | Flower                            | [56]       |
|                       | β-Myrcene                       | Flower, leaves                    | [53]       |
|                       | Acacetin                        | Leaves                            | [58]       |
|                       | Apigenin                        | Fruit                             | [59]       |
|                       | Cosmosiin                       | Leaves                            | [28, 58]   |
|                       | Diosmetin                       | Flavedo                           | [58]       |
|                       | Diosmin                         | Flavedo, fruit juice              | [58]       |
|                       | Eriocitrin                      | Albedo                            | [58]       |
|                       | Hesperidin                      | Peel, fruit juice                 | [60]       |
|                       | Honyucitrin                     | Root bark                         | [58]       |
|                       | Isoisoumenetin                  | Peel                              | [58]       |
|                       | Luteolin                        | Fruit juice, leaves, peel         | [58]       |
|                       | Naringenin                      | Fruits peel                       | [61, 62]   |
|                       | Naringin                        | Fruits peel                       | [61–65]    |
|                       | Naringin 4'-glucoside           | Flavedo, albedo                   | [28, 58]   |
|                       | Narirutin                       | Fruit juice, peel, leaves         | [60]       |
|                       | Neodiosmin                      | Fruit juice, peel                 | [28, 58]   |
|                       | Neoeicocitrin                   | Fruit juice, peel, leaves         | [58]       |
|                       | Neohesperidin                   | Fruit juice, peel, leaves         | [60]       |
|                       | Neoponcinir                     | Fruit juice, peel                 | [66]       |
|                       | Nobleitin                       | Peel                              | [58]       |
|                       | Poncinir                        | Albedo, leaves                    | [66]       |
|                       | Quercetin                       | Fruit juice                       | [28, 58]   |
|                       | Rutin                           | Peel, leaves                      | [58]       |
|                       | Tangeretin                      | Fruit peel                        | [67]       |
|                       | Nobleitin                       | Fruit peel                        | [67]       |
|                       | Apigenin trimethyl ether        | Fruit peel                        | [67]       |
|                       | Sinensetin                      | Fruit peel                        | [67]       |
|                       | 5,7,3',4'-Tetramethoxyflavone   | Fruit peel                        | [67]       |
|                       | 5,7,8,3',4'-Penta-methoxyflavone| Fruit peel                        | [67]       |
| Phenolics             | Ferulic acid                    | Fruit                             | [59]       |
|                       | 4-Hydroxycinnamic acid          | Fruit                             | [59]       |
|                       | Caffeic acid                    | Seed                              | [28]       |
|                       | Gallic acid                     | Fruit                             | [59, 66]   |
|                       | Vanillic acid                   | Fruit                             | [59]       |
| Steroids              | β-Sitosterol                    | Peel, root, fruit                 | [21, 65, 68] |
|                       | Campesterol                     | Peel, root                        | [21, 68]   |
|                       | Daucosterol                     | Peel, root                        | [21, 68]   |
|                       | Stigmasterol                    | Peel, root                        | [21, 68]   |
| Triterpenes           | Deacetylnomilin                 | Seed                              | [28]       |
|                       | Deoxyxilimonin                  | Seed, fruit, pulp                 | [28]       |
|                       | Limonin                         | Seeds, fruit, peel, leaves        | [69]       |
|                       | Nomilin glucoside               | Peel                              | [28]       |
|                       | Nomilnic acid                   | Seed                              | [28]       |
|                       | Obacunone                       | Leaves, seed, fruit pulp          | [28]       |
|                       | Obacunone glucoside             | Seed                              | [28]       |
Buntanbismine: R₁=H, R₂=H
5-Acetyl-buntanbismine; R₁=Ac, R₂=H
1,5-Diacetyl-buntanbismine: R₁=Ac, R₂=Ac

Citbismine-A: R₁=OH, R₂=H, R₃=H
Citbismine-B: R₁=OCH₃, R₂=OH, R₃=H
Citbismine-C: R₁=OCH₃, R₂=OH, R₃=H₃

Figure 2: Chemical structures of some alkaloids from *C. maxima*. 
5. Pharmacological Activities

Various studies have been performed regarding the pharmacological effects of *C. maxima* extracts and their isolated compounds. Modern pharmacological studies confirm the traditional efficacy of this plant as an antiepileptic, antidepressant, and anti-inflammatory agent. The plant is highly potent for treating anxiety, depression, Alzheimer’s disease (AD), and other neurological diseases. The plant also exhibits additional antioxidant, analgesic, hepatoprotective, antimicrobial, and anticancer activities. In this review, we collected the available information and described major pharmacological properties like antioxidant, antidepressant, anxiolytic, anti-Alzheimer’s disease, antitumor, insecticidal, antidiabetic, antimicrobial, hepatoprotective, anti-obesity, anti-inflammatory, and analgesic activities.

5.1. Antioxidant Activity. Dulay et al. studied the antioxidant activity of leaf extracts of *C. maxima* along with two other plants, i.e., *C. microcarpa*, and *C. aurantium* by 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay where *C. microcarpa* showed the highest scavenging activity of 48.67% followed by *C. maxima* having 43.51%, and *C. aurantium* had the lowest antioxidant capacity [80]. Fidrianny et al. also reported the antioxidant activity of its leaves, peel, and cortex extracts by DPPH and phosphomolybdenum assays. Data showed that the ethyl acetate extract of cortex exhibited the lowest IC50 value of 0.68 μL in DPPH scavenging activity, while ethyl acetate leaf extracts exhibited an IC50 value of 101.36 μL/mL in the phosphomolybdenum assay [81].

The in vivo antioxidant activity of methanolic leaf extract (200 and 400 mg/kg, b.w.) was evaluated against paracetamol-induced hepatotoxicity in Wistar albino rats. Leaf extract at 400 mg/kg b.w. showed reduced lipid peroxidation in paracetamol-treated rat liver as compared to that of saline control. It was also able to restore the depleted catalase and reduce glutathione levels in the paracetamol-intoxicated rat liver to the normal levels, indicating the in vivo antioxidant potential of extracts in paracetamol challenged rats [82]. The freeze-dried fruit extract of *C. maxima* exhibited 6609 μ-mol Fe2+/L antioxidant power through the ferric-reducing antioxidant powder (FRAP) assay which is very similar to the standard drug ascorbic acid [83]. The presence of major phytochemicals might be the reason for showing significant antioxidant activity by *C. maxima* extracts [14, 84, 85].

5.2. Antidepressant Activity. The aqueous leaf extracts (100, 200, and 300 mg/kg) of *C. maxima* were evaluated in mice for their antidepressant potential using different models. Fluoxetine (20 mg/kg, i.p.) and imipramine (30 mg/kg, i.p.) were used as standard drugs. The aqueous leaf extracts reduced the immobility time in both the tail suspension test (TST) and the forced swimming test (FST). The exact mechanism for exhibiting antidepressants was not reported, but it might be due to enhancement of norepinephrine neurotransmission in mice [20]. Similarly, the per-oral administration of ethanolic extracts (200 and 400 mg/kg) of *C. maxima* in mice increased the number of rearing in both the TST and FST models while imipramine (1 mg/kg) noticeably reduced the immobility time [86].

Hesperidin and naringin were evaluated against antidepressant activity using the FST and TST models. Both compounds exhibited significant antidepressant activity [87, 88]. The antidepressant effects of plant extracts might be due to the interaction with the serotonergic 5-HT1A and κ-opioid receptors [89, 90]. It was concluded that *C. maxima* extract was useful in its motor-stimulating effects.

5.3. Anti-Alzheimer’s Disease Activity. Alzheimer’s disease is a neurodegenerative progressive disease that occurs in the elderly population. During the experiments performed using Ellman’s colorimetric and scopolamine-induced Alzheimer’s methods, ethanolic, hexane, ethyl acetate, and aqueous extracts of *C. maxima* fruit peel exhibited potent anti-Alzheimer’s activity. Similarly, it was found that the brain acetylcholinesterase level was decreased by leaf extract and showed anti-Alzheimer’s activity [14, 90].

Naringin (40 and 80 mg/kg, p.o.) showed anti-Alzheimer’s activity in colchicine tempted cognitive impaired rats through the elevated plus maze and Morris water maze methods. Colchicine (15 μg/5mL) was given intracerebroventricularly which causes poor memory retention and reduces acetylcholinesterase activity in both the models [88]. The anti-Alzheimer’s activity might be due to the development in the cognitive act and diminished oxidative stress by lowering malondialdehyde and nitrite levels. Also, it might be due to the renewal of superoxide dismutase and catalase, and glutathione S-transferase, and a reduction in glutathione as well as the acetylcholinesterase level in tested mice [91].

5.4. Anticancer and Antitumor Activity. The leaf extract of *C. maxima* tested against Ehrlich ascites carcinoma (EAC) models in Swiss albino rats decreased the white blood cell...
Figure 4: Chemical structures of some coumarins from *C. maxima.*
Figure 5: Chemical structures of some flavonoids from C. maxima.

Acacetin  Apigenin  Cosmosiin  Diosmetin
Hesperidin  Naringenin  Naringin  Neohesperidin  Eriocitrin
Luteolin  Nobiletin  Quercetin

Figure 6: Chemical structures of phenolic acids from C. maxima.

Caffeic acid  4-Hydroxycinnamic acid  Ferulic acid
Gallic acid  Vanillic acid
(WBC) count and increased the lifespan. The biochemical parameters were also in the normal level as compared to the control group [92]. The methanolic extract of the leaves and its fractions in n-hexane, n-butanol, chloroform, ethyl acetate, and water were tested in normal cells and different cancerous cells through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium (MTT) assay. Importantly, the chloroform fraction of leaf extract reduced the survival of HeLa cells [93].

Naringin exhibited potent anticancer activity in various experiments. Naringin (10, 25, and 35 mg/kg i.p.), when treated on rats bearing Walker 256 carcinosarcoma (W256) reduced tumor growth by 75% and TNF-α and IL-6 levels decreased in comparison with the control [94, 95]. Naringenin also exhibited cell proliferation and cell migration in B16F10 murine and SK-MEL-28 human melanoma cells. Hesperidin exhibited chemopreventive effects against an azoxymethane (AOM) induced carcinogenesis in the mouse colon. It was found to have significant reducing power for the multiplicities of AOM-induced aberrant crypt foci (ACF) and tumor incidence. It also decreased the proliferative marker proliferating cell nuclear antigen (PCNA) against AOM-induced colon carcinogenesis [96, 97]. The presence of flavonoids, limonoids, alkaloids, tannins, saponin, and bioflavonoids plays a prominent role in cancer prevention [59, 92, 98].

The anticancer activity of naringenin loaded liquid crystalline nanoparticles (LCNs) was evaluated against human lung epithelial carcinoma (A549) and airway epithelium derived basal cells (BCI-NS1.1). Mainly antiproliferative, antimigratory, and anti- colony formation activity were studied in which naringenin LCNs showed its significant anticancer properties by inhibiting the migratory and proliferation properties of cells [99].

5.5. Antidiabetic Activity. The in vitro enzyme inhibitory activity of C. maxima fruit juice was examined against α-glucosidase and α-amylase. The percentage inhibition by fruit juice for α-amylase was 75.55%–79.75% and, for α-glucosidase, it was 70.68%–72.83% [100]. The hypoglycaemic property of fruit juice was examined in the streptozotocin (STZ)-induced diabetes mellitus model. The glucose level was lowered in experimental rats than in control rats which is due to the peripheral utilization of glucose or inhibition of gluconeogenic enzymes [23].

The antidiabetic activity of the leaf extracts (200 and 400 mg/kg, b.w.) was evaluated in STZ (65 mg/kg) induced diabetic rats using glibenclamide (0.5 mg/kg, p.o) as the reference standard. The blood glucose level and serum biochemical parameters were measured and found to be normalized in experimental rats than in the control group [101]. The antidiabetic effect of neohesperidin on α-amylase and α-glucosidase improved postprandial hyperglycemic conditions [102]. The antioxidant activity of plants may lead to their defensive effects against chronic metabolic disorders [103].

The antidiabetic activity of methanolic and ethanolic leaf extracts (100 and 200 mg/kg of each extract) of C. maxima was also evaluated against the alloxan (90 mg/kg b.w.) induced diabetes model in mice while glibenclamide (5 mg/kg, p.o) was used as the standard. The plasma glucose level and parameters of serum lipid profile, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and C-reactive protein (CRP) were measured and found to be inhibited by the leaf extract in experimental mice as compared to control mice. This finding suggests that both extracts have significant hypoglycemic effects and can ameliorate the altered lipid profile in diabetic mice. Moreover, the results suggested that the extracts of C. maxima leaf can restore altered levels of liver function enzymes and CRP in diabetic mice, highlighting the hepatoprotective and cardioprotective potentiality of this plant [104].

5.6. Antimicrobial Activity. The antibacterial activity of C. maxima has been widely studied. The ethanolic leaf extract exhibited antibacterial activity against Pseudomonas aeruginosa and Escherichia coli [17]. The ethanolic pulp and seed extracts also exhibited antibacterial activity against Bacillus subtilis, Staphylococcus aureus, and Escherichia coli in the disc diffusion method [105]. In another study, the methanolic extracts of the leaves, seeds, fruits peel, and barks were tested against Escherichia coli, Klebsiella pneumonia, and Staphylococcus aureus. Pulp extract showed the highest zone of inhibition (ZOI) of 26 mm in Klebsiella pneumonia, while none of the other extracts showed significant ZOI. The aqueous extract of the pulp also showed highest antibacterial activity (ZOI of 27 mm) against Staphylococcus aureus [106]. The presence of naringenin and hesperidin might be responsible for its antibacterial activity. The antibacterial activity of hesperidin against Gram-positive and Gram-negative bacteria has already been established [107]. The essential oils from C. maxima also demonstrated antibacterial activity against Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus licheniformis, and Bacillus altitudinis in the broth dilution method [108].
The significant antifungal activity of ethanolic and aqueous leaf extracts against Fusarium moniliforme, Aspergillus niger, and Mucor plumbeus fungus was reported by Hemalatha through the agar-well diffusion and disc diffusion methods [109]. Similarly, Jing et al. reported that limonene is effective against Aspergillus niger, A. flavus, A. fumigatus, A. terreus, A. parasiticus, Penicillium chrysogenum, P. digitatum, P. italicum, P. expansum, Fusarium oxysporum, F. proliferatum, and Alternaria alternata [110].

5.7. Hepatoprotective Activity. C. maxima leaf and peel extracts revealed liver protective effect in carbon tetrachloride-induced hepatotoxicity in Wistar rats. Significant reduction of aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) levels in experimental rats proved its hepatoprotective activity [111, 112]. In another study, hepatoprotective effects of C. maxima methanolic leaf extract (200 mg/kg, b.w.) was examined in paracetamol-induced hepatotoxicity in rats. In this study, leaf extracts were administered for 7 days, paracetamol (2 g/kg) was administered at 5th day, and silymarin (100 mg/kg, b.w.) was used as the standard drug. Liver was extracted and liver function markers, total bilirubin, total protein in blood serums, and hepatic antioxidants in liver homogenate were evaluated and found normal as compared to the control group [113]. Leaf extracts having antioxidant property might be responsible to decrease the distortion of hepatocytes by elevating the hepatic antioxidant enzymes levels [31].

5.8. Anti-obesity Activity. The anti-obesity activity of ethanolic leaf extract (200 and 400 mg/kg) against olanzapine-induced obesity and cafeteria diet-induced obesity in rats. Body weight, body temperature, and serum parameters were evaluated and found significantly decreased in their values as compared to the obese control group [114]. Ding et al. fed the C. maxima ethanolic peel extract to the mice along with Chow diet for 8 weeks. The diet lowered the weight, decreased fasting blood glucose levels, and also reduced liver lipid and serum insulin levels [115]. Hesperidin also regulates the lipid and glucose metabolism and indirectly facilitates NF-κB signalling way to control inflammation which helps in controlling obesity [116, 117].

5.9. Analgesic and Anti-Inflammatory Activity. Various parts of C. maxima have shown analgesic and anti-inflammatory properties. The analgesic property of the methanolic extract of its peel was examined by formalin-induced licking and biting model and acetic acid-induced writhing model. The extract at a higher dose (500 mg/kg) showed satisfactory analgesic activity (73.34%) in the acetic acid-induced pain model as compared to 87.13% activity shown by standard drug diclofenac sodium at 10 mg/kg dose [118]. In another experiment, the analgesic activity of leaf, stem, and fruit was compared by using the tail-flick method in rats, acetic acid-induced writhing, and the hot plate method in mice. Results showed that the leaf extract at 300 mg/kg showed significant analgesic activity in all the models used [119]. Similarly, Kundusen et al. also showed its anti-inflammatory activity in rats when evaluated using formalin, carrageenan, and dextran-induced acute rat paw edema models. Many studies suggested that the mechanism responsible for analgesic and anti-inflammatory activity is due to inhibition of prostaglandin synthesis. Also the presence of flavonoids and their respective aglycones like hesperetin and naringenin might be the reason for the potent anti-inflammatory and analgesic activity [10, 118–120].

5.10. Other Uses. C. maxima fruits are known for their characteristic flavor, making them suitable for breakfast. The peel oil is used as a flavoring agent in food, pharmaceutical products, cosmetics, and perfumery items [25]. Due to refreshing and good-smelling properties, its essential oils are also added in toiletry and insecticidal products [121]. The pectin in rind is used in making jellies and candies, and wood can be used for making suitable tool handles [122].

6. Conclusion and Future Prospects

C. maxima offers a wide range of medicinal and nutritional uses. Almost all parts of the plant, including whole fruit, fruit pulp, fruit rind, fruit peel, juice, flower, leaf, seed, and essential oils, are traditionally used for the treatment of various diseases. A phytochemical profile showed the presence of many bioactive chemical constituents under several chemical classes including alkaloids, benzenoids, carotenoids, phenols, flavonoids, tannin, terpenoids, saponins, amino acids, and carbohydrates. Extracts of various plant parts showed numerous pharmacological properties like antioxidant, antimicrobial, analgesic, anticancer, antidiabetics, anti-inflammatory, anti-Alzheimer’s, insecticidal, anxiolytic, hepatoprotective, antimarial, and anti-obesity activities. Isolated compounds like hesperidin, limonene, naringenin, naringin, and neohesperidin have been reported to possess bioactivities like antioxidant, antidepressant, antitumor, anticancer, antimicrobial, hepatoprotective, anti-obesity, insecticidal, analgesic activity, anxiolytic, anti-Alzheimer, antiinulcer, and antiinflammatory activities. The essential oils from fruits and leaves have enhanced their use in the perfumery and cosmeceutical industry.

Despite the tremendous ethnomedicinal reports, preliminary studies, and promising results, correlations between traditional uses and pharmacological activities are still needed to be established. Bioassay-guided fractionation and isolation of compounds is needed to find more potent and novel compounds for the discovery of lead compounds and to demonstrate their molecular mechanisms to design effective herbal products and functional foods. Extensive in vivo pharmacological tests, pharmacokinetic studies, clinical trials, and toxicity studies are needed. The information regarding the therapeutic dose, dosage form, and safety of the plant products is still an area to be explored. Since the plants can easily grow in south-east Asia including Nepal and India, local farmers can be promoted for the mass cultivation of this plant and small-scale herbal pharmaceutical and juice
industries can be established. Thus, viable products and food supplements of this plant species can be designed and marketed at an international level which will ultimately uplift the economic status of the local producer.

**Abbreviations**

| Abbreviation | Meaning |
|--------------|---------|
| ABTS:        | 2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) |
| AD:          | Alzheimer’s disease |
| ALP:         | Alkaline phosphatase |
| ALT:         | Alanine transaminase |
| AST:         | Aspartate amino transferase |
| COX-2:       | Cyclooxygenase-2 |
| EAC:         | Ehrlich ascites carcinoma |
| EPM:         | Elevated plus maze test |
| FST:         | Forced swimming test |
| HDL:         | High-density lipoproteins |
| HUVEC:       | Human umbilical vein endothelial cell |
| IL-6:        | Interleukin 6 |
| iNOS:        | Inducible nitric oxide synthase |
| LDL:         | Low-density lipoproteins |
| MIC:         | Minimum inhibitory concentration |
| MTT:         | 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium |
| PPARs:       | Peroxisome proliferator-activated receptors |
| SGOT:        | Serum glutamic oxaloacetic transaminase |
| SGPT:        | Serum glutamic pyruvic transaminase |
| TNF-α:       | Tumor necrosis factor-alpha |
| ZOI:         | Zone of inhibition |
| DPPH:        | 2,2-diphenyl-1-picrylhydrazyl |
| TST:         | Tail suspension test |

**Data Availability**

No new experimental data were generated during the preparation of this review article.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest.

**Authors’ Contributions**

BS and PP conceived the idea, collected the literature information, and drafted the manuscript. HPD and PP revised the manuscript. All authors read and approved the final version of the manuscript before submission.

**References**

[1] E. S. Louzada and C. Ramadugu, “Grapefruit: history, use, and breeding,” *HortTechnology*, vol. 31, 2021.

[2] R. Susandarini, S. Subandiyah, Rugayah, B. S. Daryono, and L. H. Nugroho, “Assessment of taxonomic affinity of Indonesian pummelo (citrus maxima (Burm.) Merr.) based on morphological characters,” *American Journal of Agricultural and Biological Science*, vol. 8, 2013.

[3] T. K. Lim, *Citrus maxima. Edible Medicinal And Non-Medicinal Plants*, Springer Science and Business Media, Germany, 2012.

[4] A. Singh, “Citrus maxima (burm.) merr. a traditional medicine: its antimicrobial potential and pharmacological update for commercial exploitation in herbal drugs—a review,” *International Journal of ChemTech Research*, vol. 10, 2017.

[5] A. Singh and Navneet, “Evaluation of antimicrobial potential and phytochemical assessment of Citrus maxima burm. seeds extracts against respiratory tract pathogens,” *New York Science Journal*, vol. 9, 2016.

[6] M. W. Cheong, S. Q. Liu, W. Zhou, P. Curran, and B. Yu, “Chemical composition and sensory profile of pomelo (citrus grandis (L.) osbeck) juice,” *Food Chemistry*, vol. 135, 2012.

[7] A. Kharjul, K. Mangesh, K. Vilegave, P. Chandankar, and M. Gadiya, ”Pharmacognostic investigation on leaves of Citrus maxima (brun.) merr. (rutaceae),” *International Journal of Pharma Sciences and Research*, vol. 3, no. 12, pp. 4913–4918, 2012.

[8] P. Buachan, L. Chularojmontri, and S. K. Wattanapitayakul, “Selected activities of Citrus maxima merr. Fruits on human endothelial cells: enhancing cell migration and delaying cellular aging,” *Nutrients*, vol. 6, no. 4, pp. 1618–1634, 2014.

[9] J. P. Gautam and T. P. Gotame, “Diversity of native and exotic fruit genetic resources in Nepal,” *Journal of Nepal Agricultural Research Council*, vol. 6, pp. 44–55, 2020.

[10] S. Kundusen, M. Gupta, U. K. Mazumder, and P. K. Haldar, “Exploration of anti-inflammatory potential of Citrus limetta risco and Citrus maxima,” *J. Burm.) merr. Pharmacologyonline*, vol. 1, pp. 702–709, 2011.

[11] S. Chaudhari, G. Ruknuddin, and P. Prajapati, “Ethno medicinal values of Citrus genus: a review,” *Medical Journal of Dr. D.Y. Patil University*, vol. 9, no. 5, p. 560, 2016.

[12] J. Sidana, V. Saini, S. Daihya, P. Nain, and S. Bala, “A review on citrus— the boon of nature,” *International Journal of Pharmaceutical Sciences Review and Research*, vol. 18, no. 2, pp. 20–27, 2013.

[13] N. Thavanapong, P. Wettiyayaklung, and J. Charoenteeraboon, “Comparison of essential oils compositions of Citrus maxima merr. ped obtained by cold press and vacuum stream distillation methods and of its peel and flower extract obtained by supercritical carbon dioxide extraction method and their antimicrobial activity,” *Journal of Essential Oil Research*, vol. 22, no. 1, pp. 71–77, 2010.

[14] P. Vijayalakshmi and R. Radha, “In vitro anti-alzheimer and anti oxidant activity of the peels of Citrus maxima fruits,” *Research Journal of Pharmacology and Pharmacodynamics*, vol. 8, no. 1, p. 17, 2016.

[15] M. Borah and S. Ahmed, “A comparative study of the antibacterial activity of the ethanol extracts of Vitex negundo L., Fragaria vesca L., Terminalia arjuna and Citrus maxima,” *Asian Journal of Pharmaceutical and Biological Research*, vol. 2, no. 3, pp. 183–187, 2012.

[16] P. Vijayalakshmi and R. Radha, “Department of pharmacognosy, college of pharmacy, madras medical college, Chennai-600003, Tamilnadu, India. An overview: citrus maxima,” *Journal of Phytopharmacology*, vol. 4, no. 5, pp. 263–267, 2015.

[17] S. Das, M. Borah, and S. Ahmed, “Antibacterial activity of the ethanol extract of leaves of Citrus maxima (burm.) merr. on Escherichia coli and Pseudomonas aeruginosa,” *Asian Journal of Pharmaceutical and Clinical Research*, vol. 6, pp. 136–139, 2013.

[18] N. K. Dubey, R. Kumar, and P. Tripathi, “Global promotion of herbal medicine: India’s opportunity,” *Current Science*, vol. 86, no. 37–41, 2004.
Evidence-Based Complementary and Alternative Medicine

[19] C. Guo, J. Yang, J. Wei, Y. Li, J. Xu, and Y. Jiang, “Antioxidant activities of peel, pulp and seed fractions of common fruits as determined by FRAP assay,” *Nutrition Research*, vol. 23, no. 12, pp. 1719–1726, 2003.

[20] V. H. Potdar and S. J. Kibile, “Evaluation of antidepressant-like effect of *Citrus maxima* leaves in animal models of depression,” *Iranian Journal of Basic Medical Sciences*, vol. 14, no. 5, pp. 478–483, 2011.

[21] B. A. Arias and L. Ramón-Laca, “Pharmacological properties of *Citrus* and their ancient and medieval uses in the mediterranean region,” *Journal of Ethnopharmacology*, vol. 97, no. 1, pp. 89–95, 2005.

[22] N. Dhami, “Ethnomedicinal uses of plants in western Terai of Nepal: a case study of Dekhathbhu VDC of Kanchanpur district,” *Medicinal Plants in Nepal: An Anthology of Contemporary Research*, Ecological Society, Kathmandu, Nepal, 2008.

[23] A. Oyedepo and S. O. Babarinde, “Effects of Shaddock (*Citrus grandis*) fruit juice on glucose tolerance and lipid profile in type-II diabetic rats,” *Chemical science transactions*, vol. 2, no. 1, pp. 19–24, 2012.

[24] N. Hutadilok-Towatana, P. Chaiyamutti, K. Panthong, W. Mahabusarakam, and V. Rukkachaisirikul, “Antioxidative and free radical scavenging activities of some plants used in Thai folk medicine,” *Pharmaceutical Biology*, vol. 44, no. 3, pp. 221–228, 2006.

[25] S. M. Njorge, H. Koaze, P. N. Kajaran, and M. Sawamura, “Volatile constituents of redblush grapefruit (*Citrus paradisi*) and pummelo (*Citrus grandis*) peel essential oils from Kenya,” *Journal of Agricultural and Food Chemistry*, vol. 53, no. 25, pp. 9790–9794, 2005.

[26] H. J. Hong, J. Y. Jin, H. Yang et al., “Dangyuja (*Citrus grandis Osbeck*) peel improves lipid profiles and alleviates hypertension in rats fed a high-fat diet,” *Laboratory Animal Research*, vol. 26, no. 4, pp. 361–367, 2010.

[27] C. P. Khare, *Indian Medicinal Plants-An Illustrated Dictionary*. Indian Reprint Springer (India) Pvt. Ltd, New Delhi, India, 2007.

[28] T. P. Sawant and D. Panhekar, “A brief review on recent advances of *Citrus maxima* (Chakata),” *International Journal Of Recent Scientific Research*, vol. 8, pp. 19400–19416, 2017.

[29] P. N. Ani and H. C. Abel, “Nutrient, phytochemical, and pungent compound from *Citrus reticulata* blanco leaves,” *Pharmacological Biology*, vol. 54, no. 4, pp. 569–571, 2016.

[30] A. Alquézar, M. Rodrigo, and L. Zacarias, “Carotenoid biosynthesis and their regulation in citrus fruits,” *Tree and Forestry Science and Biotechnology*, vol. 2, no. 1, pp. 23–37, 2008.

[31] C. C. Jiang, Y. F. Zhang, Y. J. Lin, Y. Chen, and X. K. Lu, “Illumina® sequencing reveals candidate genes of carotenoid metabolism in three pummelo cultivars (*Citrus maxima*) with different pulp color,” *International Journal of Molecular Sciences*, vol. 20, no. 9, 2019.

[32] N. Tao, Y. Gao, Y. Liu, and F. Ge, “Carotenoids from the peel of shatian pummelo (*Citrus grandis* osbeck) and its antimicrobial activity,” *American-Eurasian Journal of Agricultural and Environmental Sciences*, vol. 7, no. 1, pp. 110–115, 2010.

[33] Y. Zhao, X. Yang, Y. Hu, Q. Gu, W. Chen, and J. Li, “Analysis of carotenoid components in ‘minihongyou’ [*Citrus maxima* (burm. merr.) fruit] by HPLC,” *Chinese Journal of Topical Crops*, vol. 42, pp. 546–552, 2021.

[34] W. Tian-Shung, K. Chang-Sheng, and H. Furukawa, “A new linear pyranoacridone alkaloid from *Citrus grandis*, Osbeck. *Heterocycles*.”

[35] E. Correa, W. Quiñones, and F. Echeverri, “Methyl-N-methylantranilate, a pungent compound from *Citrus reticulata* blanco leaves,” *Pharmacological Biology*, vol. 54, no. 4, pp. 569–571, 2016.

[36] A. Oyedepo and S. O. Babarinde, “Effects of Shaddock (*Citrus grandis*) fruit juice on glucose tolerance and lipid profile in type-II diabetic rats,” *Chemical science transactions*, vol. 2, no. 1, pp. 19–24, 2012.
Evidence-Based Complementary and Alternative Medicine

[53] K. Hosni, N. Zahed, R. Chrif et al., “Composition of peel essential oils from four selected tunisian citrus species: evidence for the genotypic influence,” Food Chemistry, vol. 123, no. 4, pp. 1098–1104, 2010.

[54] P. Singh, R. Shukla, B. Prakash et al., “Chemical profile, antifungal, antiaflatoxigienic and antioxidiant activity of Citrus maxima burn. and citrus sinensis (L.) Osbeck essential oils and their cyclic monoterpane, DL-limonene,” Food and Chemical Toxicology, vol. 48, no. 6, pp. 1734–1740, 2010.

[55] M. L. Lota, D. De Rocca Serra, F. Tomi, C. Jacquemond, and J. Casanova, “Volatile components of peel and leaf oils of lemon and lime species,” Journal of Agricultural and Food Chemistry, vol. 50, no. 4, pp. 796–805, 2002.

[56] F. A. Jabalpurwala, J. M. Smoot, and R. L. Rouseff, “A comparison of citrus blossom volatiles,” Phytochemistry, vol. 70, pp. 1428–1434, 2009.

[57] P. R. Vijayalakshmi, “Anti-alzheimer activity of Citrus maxima (J. burn.) Merr fruit peel extract in mice with scopolamine induced alzheimer’s disease,” International Journal of Advanced Research and Development, vol. 1, no. 4, pp. 77–82, 2016.

[58] D. Barrea, C. Bisignano, G. Ginestra et al., “Poly-methoxylated, C- and O-glycosyl flavonoids in tangelo (Citrus reticulata × Citrus paradisi) juice and their influence on antioxidant properties,” Food Chemistry, vol. 141, no. 2, pp. 1481–1488, 2013.

[59] Z. Khanam, C. H. Ching, N. Hazerra, B. Mohd, K. H. Sam, and I. U. H. Bhat, “Phytochemical analyses and DNA cleavage activity of citrus maxima fruit,” in Proceedings of the International Conference on Chemistry and Environmental Sciences Research, vol. 123, pp. 1481–1488, 2013.

[60] A. A. Damián-Reyna, J. C. González-Hernández, and M. D. C. Chávez-Parga, “Procedimientos actuales para la extracción y purificación de flavonoides cítricos,” Revista Colombiana de Biotecnología, vol. 18, no. 1, pp. 135–147, 2016.

[61] M. Mizuno, M. Inouma, M. Ohara, T. Tanaka, and M. Iwamasa, “Chemotaxonomy of the genus citrus based on polymethyloflavonenes,” Chemical and Pharmaceutical Bulletin, vol. 57, no. 534, pp. 364–370, 2002.

[62] L. M. Cordenonsi, R. M. Sponchiado, S. C. Campanharo, C. V. Garcia, R. P. Raffin, and E. E. Schapoval, “Study of flavonoides present en pomelo (Citrus maxima) by DSC, UV-VIS, IR, 1H and 13C NMR an d MS,” Drug Analytical Research, vol. 1, no. 1, pp. 31–37, 2017.

[63] A. Hakim, Jamaluddin, I. N. Loka, Sukib, and N. W. S. Prastiw, “New method for isolation of naringin compound from Citrus maxima,” Natural Resources, vol. 10, no. 08, pp. 299–304, 2019.

[64] N. Sowmya, N. Haraprasad, and B. Hema, “Exploring the total flavonoid content of peels of Citrus aurantium, Citrus maxima and Citrus sinensis using different solvents and HPLC-analysis of flavonones-Naringin and Naringenin in peels of Citrus maxima,” Journal of Pharmaceutical Innovation, vol. 8, no. 4, pp. 12–17, 2019.

[65] Y. t. Xu, K. F. Zhang, Q. j. Xie, j. x. Lin, K. x. Huan, and Y. Liao, “Chemical constituents from young fruits of Citrus maxima cv. Shatian,” Journal of Chinese medicinal materials, vol. 38, no. 9, pp. 1879–1881, 2015.

[66] H. Kelebek, “Sugars, organic acids, phenolic compositions and antioxidiant activity of grapefruit (Citrus paradisi) cultivars grown in Turkey,” Industrial Crops and Products, vol. 32, no. 3, pp. 269–274, 2010.
Evidence-Based Complementary and Alternative Medicine

Citrus maxima leaves against paracetamol induced hepatoxicity in rats," *Der Pharmacia Sinica*, vol. 2, no. 3, pp. 1–4, 2011.

B. P. Pandey, R. Thapa, and A. Upreti, "Total phenolic content, flavonoids content, antioxidant and antimicrobial activities of the leaves, peels and fruits of locally available *citrus* plants collected from kavre district of Nepal," *International Journal of Pharmacognosy & Chinese Medicine*, vol. 3, pp. 1–6, 2019.

S. Kundusen, M. Gupta, U. K. Mazumder et al., "Evaluation of in vitro antioxidant activity of Citrus limetta and Citrus maxima on reactive oxygen and nitrogen species," *Pharmacologyonline*, vol. 3, pp. 850–857, 2010.

G. Vadivukarasi and X. A. Jenitha, "In vitro studies on phytochemical analysis and antioxidant activity of *Citrus maxima*," *International Journal of Research in Pharmacology & Pharmacotherapeutics*, vol. 4, no. 2, pp. 245–251, 2015.

H. S. Sheik, N. Vedhaiyan, and S. Singaravel, "Evaluation of central nervous system activities of *Citrus maxima* leaf extract on rodents," *Journal of Applied Pharmaceutical Science*, vol. 4, no. 9, pp. 77–82, 2014.

B. Ben-Azu, E. E. Nwoke, A. O. Aderibigbe et al., "Possible neuroprotective mechanisms of action involved in the neurobehavioral property of naringin in mice," *Biomedicine & Pharmacotherapy*, vol. 109, pp. 536–546, 2019.

S. Sohi and R. Shri, "Neuropharmacological potential of the genus Citrus," *Review*, vol. 7, no. 2, pp. 1538–1548, 2018.

L. C. Souza, M. G. de Gomes, A. T. R. Goes et al., "Evidence for the involvement of the serotonergic 5-HT1A receptors in the antidepressant-like effect caused by hesperidin in mice," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 40, no. 1, pp. 103–109, 2013.

A. Roobbakhsh, H. Parhiz, F. Soltani, R. Rezaee, and M. Iranshahi, "Neuropharmacological properties and pharmacokinetics of the citrus flavonoids hesperidin and hesperetin—a mini-review," *Life Sciences*, vol. 113, no. 1–2, pp. 1–6, 2014.

A. Kumar, S. Dogra, and A. Prakash, "Protective effect of naringin, a citrus flavonoid, against colchicine-induced cognitive dysfunction and oxidative damage in rats," *Journal of Medicinal Food*, vol. 13, no. 4, pp. 976–984, 2010.

S. Kundusen, M. Gupta, U. K. Mazumder, P. K. Haldar, P. Saha, and A. Bala, "Antitumor activity of citrus maxima (burm.) merr. Leaves in ehrlich's ascites carcinoma cell-treated mice," *ISRN Pharmacology*, vol. 2011, pp. 1–6, 2011.

H. Kim, J. Y. Moon, A. Mosaicid, and S. K. Cho, "Induction of apoptosis in human cervical carcinoma lica cells by polymethoxylated flavone-rich *Citrus grandis* osbeck (dangyuja) leaf extract," *Food and Chemical Toxicology*, vol. 48, no. 8–9, pp. 2435–2442, 2010.

P. Sharma, V. Kumar, and P. Guleria, "Naringin: biosynthesis and pharmaceutical applications," *Indian Journal of Pharmaceutical Sciences*, vol. 81, no. 6, pp. 988–999, 2019.

C. A. Camargo, M. C. C. Gomes-Marcondes, N. C. Wutzki, and H. Aoyama, "Naringin inhibits tumor growth and reduces interleukin-6 and tumor necrosis factor α levels in rats with Walker 256 carcinosarcoma," *Anticancer Research*, vol. 32, no. 1, pp. 129–133, 2012.

G. Saiprasad, P. Chitra, R. Manikandan, and G. Sudhendiran, "Hesperidin alleviates oxidative stress and downregulates the expressions of proliferative and inflammatory markers in azoxymethane-induced experimental colon carcinogenesis in mice," *Inflammation Research*, vol. 62, no. 4, pp. 425–440, 2013.

D. Stanisic, A. F. Costa, W. J. Favaro, L. Tasic, A. B. Seabra, and N. Duran, "Anticancer activities of hesperidin and hesperetin in vivo and their potentiality against bladder cancer," *Journal of Nanomedicine & Nanotechnology*, vol. 9, no. 5, 2018.

S. A. Nair, R. K. Sr, A. S. Nair, and S. Baby, "Citrus peels prevent cancer," *Phytomedicine*, vol. 50, pp. 231–237, 2018.

R. Wadhwa, K. R. Paudel, L. H. Chin et al., "Anti-inflammatory and anticancer activities of naringenin-loaded liquid crystalline nanoparticles in vitro," *Journal of Food Biochemistry*, vol. 45, no. 1, 2021.

A. Abirami, G. Nagarani, and P. Siddharaju, "In vitro antioxidant, anti-diabetic, cholinesterase and tyrosinase inhibitory potential of fresh juice from *Citrus hystrix* and *C. maxima* fruits," *Food Science and Human Wellness*, vol. 3, no. 1, pp. 16–25, 2014.

S. Kundusen, M. Gupta, U. K. Mazumder et al., "Anti-hyperglycemic effect and antioxidant property of *citrus maxima* leaf in streptozotocininduced diabetic rats," *ISRN Endocrinology*, vol. 2011, no. 4, pp. 1–6, 2011.

D. Sinha, T. Satapathy, P. Jain et al., "In vitro anti diabetic effect of neohesperidin," *Journal of Drug Delivery and Therapeutics*, vol. 9, no. 6, pp. 102–109, 2019.

S. K. Reshmi, H. K. Manonmani, J. R. Manjunatha, and M. N. Shashirekha, "Identification of bioactive compound from *Citrus maxima* fruit against carbohydrate-hydrolysing enzymes," *Current Science*, vol. 114, no. 10, pp. 2099–2105, 2018.

A. Islam, M. N. Tasnin, M. W. Bari, M. I. Hossain, and M. A. Islam, "Vitro antioxidant and in vivo anti diabetic properties of *Citrus maxima* leaf extracts in alloxan-induced swiss albino diabetic mice," *Asian Food Science Journal*, vol. 20, 2021.

M. Sahlan, V. Damayanti, D. Tristantini, H. Hermansyah, A. Wijanarko, and Y. Olivia, "Antimicrobial activities of pomelo (Citrus maxima) seed and pulp ethanolic extract," *AIP Conference Proceedings*, vol. 1933, pp. 10–16, 2018.

S. Yathider, "A comparative study of antimicrobial activity of *Citrus maxima* and *Citrus aurantium* plant extracts," *International Journal of Recent Scientific Research*, vol. 8, no. 7, pp. 18507–18509, 2017.

A. Corciovia, C. Ciobanu, A. Poiata et al., "Antibacterial and antioxidant properties of hesperidin: β-cyclodextrin complexes obtained by different techniques," *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, vol. 81, pp. 71–84, 2015.

Y. Chen, T. Li, J. Bai et al., "Chemical composition and antibacterial activity of the essential oil of *Citrus maxima* (burm.) merr. Cv. shatian Yu," *Journal of Biologically Active Products from Nature*, vol. 8, no. 4, pp. 228–233, 2018.

K. Hemalatha, "In-vitro anti-bacterial and anti fungal activities of *Citrus maxima*," *International Journal of Science and Research*, vol. 8, no. 2, pp. 1597–1604, 2019.

L. Jing, Z. Lei, L. Li et al., "Antifungal activity of citrus essential oils," *Journal of Agricultural and Food Chemistry*, vol. 62, no. 14, pp. 3011–3033, 2014.

D. L. Feksa, R. P. Coelho, A. Aparecida da Costa Gullich, E. S. Dal Ponte, J. da Costa Escobar Piccoli, and V. Manfredini, "Extract of *Citrus maxima* (pummelo) leaves improve hepatoprotective activity in wistar rats submitted to the induction of non-alcoholic hepatic steatosis," *Biomedicine & Pharmacotherapy*, vol. 98, pp. 338–346, 2018.

M. R. H. Chowdhury, M. A. T. Sagor, N. Tabassum, M. A. Potol, H. Hossain, and M. A. Alam, "Supplementation
of *Citrus maxima* peel powder prevented oxidative stress, fibrosis, and hepatic damage in carbon tetrachloride (CCl4) treated rats,” *Evidence-based Complementary and Alternative Medicine: eCAM*, vol. 2015, Article ID 598179, 10 pages, 2015.

[113] J. Tabeshpour, H. Hosseinzadeh, M. Hashemzaei, and G. Karimi, “A review of the hepatoprotective effects of hesperidin, a flavanon glycoside in citrus fruits, against natural and chemical toxicities,” *DARU. Journal of Pharmaceutical Sciences*, vol. 28, no. 1, pp. 305–317, 2020.

[114] S. S. Dinesh and K. Hegde, “Antiobesity activity of ethanolic extract of *Citrus maxima* leaves on cafeteria diet induced and drug induced obese rats,” *Research Journal of Pharmacy and Technology*, vol. 9, no. 7, pp. 907–912, 2016.

[115] X. Ding, L. Guo, Y. Zhang et al., “Extracts of pomelo peels prevent high-fat diet-induced metabolic disorders in C57Bl/6 mice through activating the PPARα and GLUT4 pathway,” *PLoS One*, vol. 8, no. 10, Article ID e77915, 2013.

[116] H. Xiong, J. Wang, Q. Ran et al., “Hesperidin: a therapeutic agent for obesity,” *Drug Design, Development and Therapy*, vol. 13, pp. 3855–3866, 2019.

[117] S. Akiyama, S. I. Katsumata, K. Suzuki, Y. Ishimi, J. Wu, and M. Uehara, “Dietary hesperidin exerts hypoglycemic and hypolipidemic effects in streptozotocin-induced marginal type 1 diabetic rats,” *Journal of Clinical Biochemistry & Nutrition*, vol. 46, pp. 87–92, 2010.

[118] M. Ibrahim, M. Nurul Amin, M. S. Millat et al., “Methanolic extract of peel of *Citrus maxima* fruits exhibit analgesic, CNS depressant and anti-inflammatory activities in swiss albino mice,” *Biology, Engineering, Medicine and Science Reports*, vol. 4, no. 1, pp. 07–11, 2018.

[119] A. Shivananda, D. Muralidhara Rao, and K. N. Jayaveera, "Analgesic and anti-inflammatory activities of *Citrus maxima* (j.burm) merr in animal models," *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, vol. 4, no. 2, pp. 1800–1810, 2013.

[120] P. Malleshappa, R. C. Kumaran, K. Venkatarangaiah, and S. Parveen, "Peels of *Citrus* fruits: a potential source of anti-inflammatory and anti-nociceptive agents," *Pharmacognosy Journal*, vol. 10, 2018.

[121] L. Biao, S. Rui, X. Zhi, Y. Min, L. Shaoxiong, and Z. Lili, "Extraction and insecticidal activities of limonin in peel of *Citrus maxima*," *Chinese Agriculture Science Bull.*, vol. 1, 2012.

[122] C. Orwa, A. Mutua, R. Kindt, R. Jamnadass, and A. Simons, *Agroforestry Database: A Tree Reference and Selection Guide Version 4.0*, World Agroforestry Centre, Nairobi, Kenya, 2009.