Chemical Content and Pharmacology of Sweet Orange (*Citrus sinensis*) Fruit Peel: A Review

Triyono Mojo[1], *Sutrisno*[1,*], *and Siti* Marfuah[1]

[1]Departement of Chemistry, Faculty of Mathematics and Science, Universitas Negeri Malang, Jl. Semarang No. 5 Malang 65145, Indonesia

Abstract. The sweet orange (*Citrus sinensis*) fruit peel is one of the often overlooked part of the sweet orange plant. However, recent research indicates that sweet orange peel possesses various bioactive properties and intriguing health benefits. The purpose of this article is to provide a comprehensive overview of the chemical compounds, pharmacological activities, and potential development of sweet orange peel, serving as an introduction to further research. Sweet orange peel contains a variety of chemical compounds, including essential oils, flavonoids, carotenoids, steroids, terpenoids, alkane groups, and ethyl esters. These chemical compositions confer antioxidant properties to sweet orange peel, which can protect the body from oxidative damage caused by free radicals. In vivo and in vitro studies have demonstrated that sweet orange peel extracts exhibit strong antioxidant activity and may aid in preventing degenerative diseases such as cancer. Additionally, sweet orange peel shows potential antimicrobial activity. Certain compounds in sweet orange peel have proven effective against various types of bacteria and pathogenic fungi.

1 Introduction

Sweet orange is considered one of the most beloved and popular fruits worldwide. Its sweet taste when ripe is a unique attraction for consumption by people of all ages, from children to adults. This has led to a large market demand, automatically increasing the commodity value for this plant. The global production of oranges is estimated at 115 million tons each year [1]. Another reason why sweet oranges are a preferred choice for consumption is the presence of active compounds such as phenolics, flavonoids, carotenoids, vitamin C, and polysaccharides, which play crucial roles in human nutrition [2–4]. Additionally, it contains folate and thiamine (vitamin B), contributing to nutritional needs [5].

The high level of sweet orange production poses another problem, namely that the consumed part of the fruit is only the flesh, leaving the fruit peel as a significant waste. If not properly managed, this large amount of wast[1]e can contribute to environmental pollution. However, this overlooked fruit peel still contains active compounds comparable to the fruit flesh. Several studies have been reported on the peel of sweet oranges, covering chemical components such as essential oils, flavonoids, carotenoids, steroids, terpenoids, alkane groups, and ethyl esters. Additionally, pharmacological activities including antioxidant, anticancer, antimicrobial, and anti-inflammatory properties have been investigated. These

* Corresponding author: sutrisno.kimia@um.ac.id

aspects will be the focus of discussion in this article, aiming to provide a comprehensive overview of the chemical compounds, pharmacological activities, and potential development of sweet orange peel. This serves as an introduction to further research, with the goal of transforming what has traditionally been considered waste into a product with commercial value.

2 Method

The method employed in this study is based on a literature review, utilizing book searches, journals, and scientific works through databases such as Google Scholar and Online Library. The search was conducted using keywords such as *Citrus sinensis*, chemical content, and pharmacological activities. This approach allowed for a comprehensive exploration of existing knowledge and research related to the chemical composition and pharmacological activities associated with *Citrus sinensis*.

3 Taxonomy and Morphology

The sweet orange is a plant belonging to the Rutaceae family. Common characteristics of this plant include reaching a tree height of 3-10 meters, having short thorns almost all over the plant, leaf stalks measuring about 0.5-3.5 cm in length with varying leaf shapes (elliptical, elongated with blunt pointed tips, and egg-shaped). The fruit is round in shape, green when young, and turns yellow or orange when mature or ready for harvesting, with the edible flesh being orangish-yellow in color [6]. The classification of sweet orange is as follows:

Kingdom	: Plantae
Subkingdom	: Tracheobionta
Superdivision	: Spermatophyta
Division	: Magnoliophyta
Class	: Magnoliopsida
Subclass	: Rosidae
Order	: Sapindales
Family	: Rutaceae
Genus	: Citrus
Species	: *Citrus sinensis* [7]

Fig. 1. Sweet orange plants, fruit, and peel.

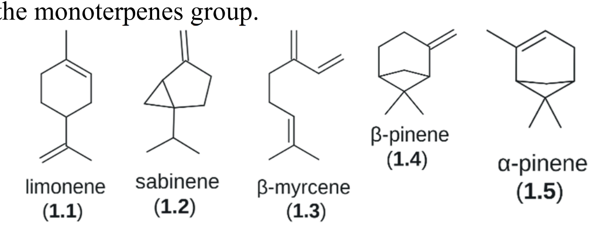
The orange fruit generally consists of two main parts: the peel and the fruit flesh. The outermost part of the orange fruit is called the peel. The peel is divided into two parts: albedo and flavedo. The inner layer of the peel has a spongy tissue and is called albedo, while the outermost layer of the peel contains oil sacs and chromoplasts and is called flavedo. The edible part of the fruit is the fruit flesh or endocarp. Within the endocarp, there are fruit juice sacs with thin layers or walls called carpels or locules [8].

4 Chemical Constituents

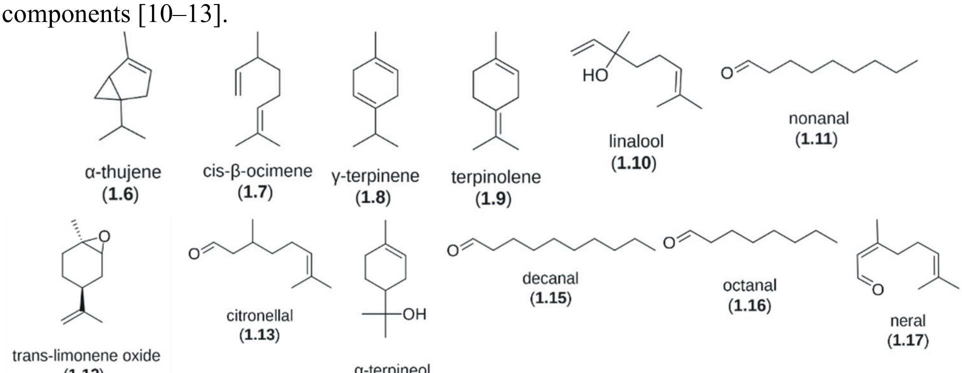
The chemical content of sweet orange peels has been reported. Sweet orange peels contain various chemical compounds, with secondary metabolites taking the focus in this discussion. The compounds present in sweet orange peels consist of essential oils, flavonoid compounds, steroids, terpenoids, alkanes, and ethyl ester.

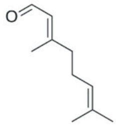
4.1 Essential Oil

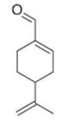
Based on the conducted research, it is stated that sweet orange peels contain essential oil, with the highest oil content in sweet orange peels being limonene (**2.1.1**) (98.238%), and other identified oil contents including sabinene (**2.1.2**) (0.071%), β-myrcene (**2.1.3**) (1.169%), β-pinene (**2.1.4**) (0.0032%), and α-pinene (**2.1.5**) (0.548%) [9]. All of these are categorized into the monoterpenes group.

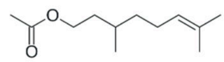


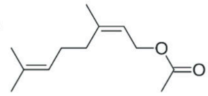
It should be noted that other identifications of essential oils from sweet orange peel have indicated the presence of the monoterpenes group, namely, α-thujene (**1.6**), α-pinene (**1.5**), sabinene (**1.2**), β-myrcene (**1.3**), limonene (**1.1**), cis-β-ocimene (**1.7**), γ-terpinene (**1.8**), and terpinolene (**2.1.9**), as well as the substituted monoterpenes group, namely, linalool (**1.10**), nonanal (**1.11**), trans-limonene oxide (**1.12**), citronellal (**1.13**), α-terpineol (**1.14**), decanal (**1.15**), octanal (**1.16**), neral (**1.17**), geranial (**1.18**), perillaldehyde (**1.19**), citronellyl acetate (**1.20**), neryl acetate (**1.21**), α-copaene (**1.22**), β-cubebene (**1.23**), dodecanal (**1.24**), germacrene D (**1.25**), valencene (**1.26**), and nootkatone (**1.27**), with limonene being stated as the major component of the essential oil with the highest composition compared to other oil components [10–13].

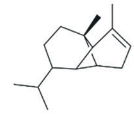


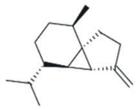

geranial (**1.18**)


perillaldehyde (**1.19**)

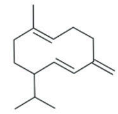

citronellyl acetate (**1.20**)

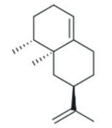

neryl acetate (**1.21**)

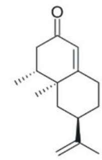

α-copaene (**1.22**)


β-cubebene (**1.23**)


dodecanal (**1.24**)

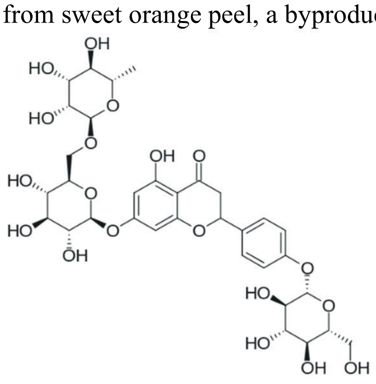

germacrene D (**1.25**)

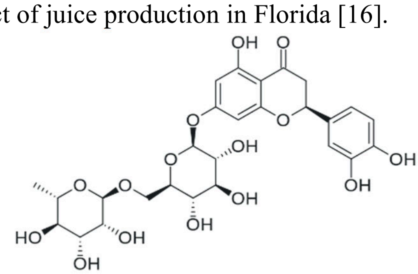

valencene (**1.26**)

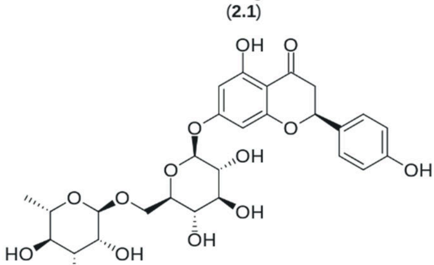

nootkatone (**1.27**)

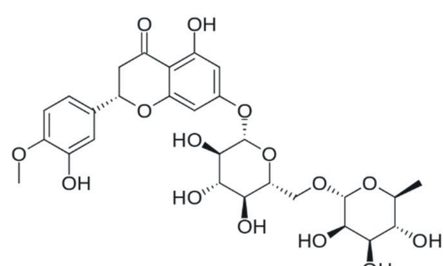
4.2 Flavonoids

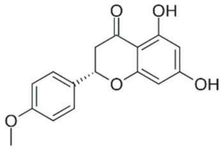
Flavonoids are secondary metabolite components that are reported to be commonly found in sweet orange peels and play a crucial role in the distinct citrus aroma. From conducted research, it has been reported that sweet orange peels extracted with dimethyl sulfoxide (DMSO)/methanol (v/v) and the squeezed juice from the skin of sweet oranges indicates the presence of a group of flavonoids, namely narirutin 4'-glucoside (**2.1**), eriocitrin (**2.2**), narirutin (**2.3**), hesperidin (**2.4**), isosakuranetin (**2.5**), sinensetin (**2.6**), quercetagetin/gossypetin (**2.7**), nobiletin (**2.8**), 3,5,6,7,8,3',4'-heptamethoxyflavone (**2.9**), tangeritin/5-hydroxy-3,7,8,3',4'-pentamethoxyflavone (**2.10**) [14,15]. Chrysoeriol (**2.11**), limocitrin (**2.12**), and limocitrol (**2.13**), which is a flavonol glycoside, was also identified in molasses from sweet orange peel, a byproduct of juice production in Florida [16].


narirutin 4'-glucoside (**2.1**)

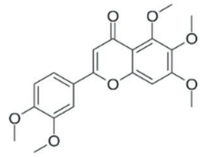

eriocitrin (**2.2**)


narirutin (**2.3**)

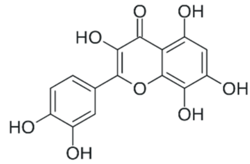

hesperidin (**2.4**)



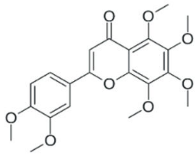
isosakuranetin
(**2.5**)



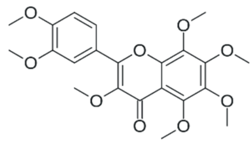
sinensetin
(**2.6**)



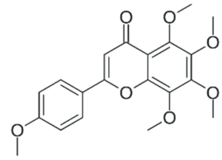
quarcetagetin/gossypetin
(**2.7**)



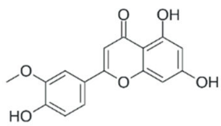
nobiletin
(**2.8**)



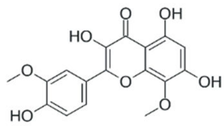
3,5,6,7,8,3',4'-heptamethoxyflavone
(**2.9**)



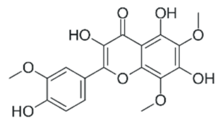
tangeritin
(**2.10**)



Chrysoeriol
(**2.11**)

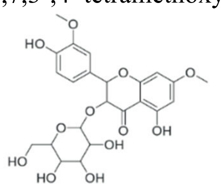


limocitrin
(**2.12**)

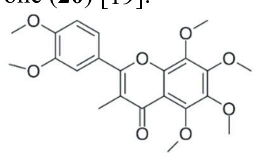


limocitrol
(**2.13**)

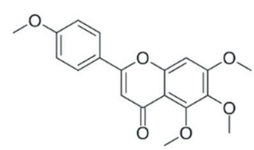
Sweet orange peels extracted using hot methanol solvent, then isolated with silica gel column chromatography, indicate the compound's character as 3,5,4'-trihydroxy-7,3'-dimethoxy flavanone 3-O-β-glucoside (**2.14**) [17]. Nobiletin (**2.8**), tangeretin (**2.10**), 3,5,6,7,8,3',4'-heptamethoxyflavone (**2.15**), and 5,6,7,4'–tetramethoxyflavone (**2.16**), which are also part of the flavonoid group, can be isolated and characterized using supercritical fluid chromatography (SFC) techniques [14,18]. Additionally, a group of polymethoxyflavones flavonoids that have been successfully identified from sweet orange peel extracts includes Heptamethoxyflavone (**2.15**), tangeretin (**2.10**), 5,6,7,4'-Tetramethoxyflavone (**2.16**), nobiletin (**2.14**), sinensetin (**2.6**), Demethyltangeretin (**2.17**), 5-Hydroxy-6,7,4'-trimethoxyflavone (**2.18**), 5-Hydroxy-3,6,7,3',4'-pentamethoxyflavone (**2.19**), and 5-Hydroxy-6,7,3',4'-tetramethoxyflavone (**20**) [19].



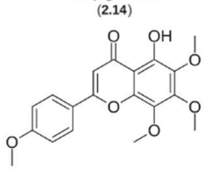
3,5,4'-trihydroxy-7,3'-dimethoxy flavanone
3-O-β-glucoside
(**2.14**)



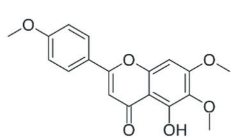
heptamethoxyflavone
(**2.15**)



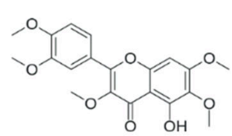
5,6,7,4'–tetramethoxyflavone
(**2.16**)



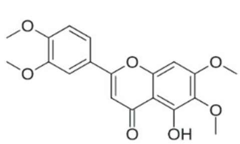
demethyltangeretin
(**2.17**)



5-hydroxy-6,7,4'-trimethoxyflavon
(**2.18**)



5-Hydroxy-3,6,7,3',4'-pentamethoxyflavon
(**2.19**)

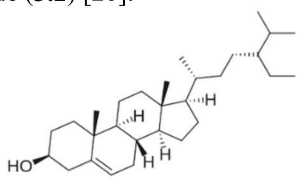


5-Hydroxy-6,7,3',4'-tetramethoxyflavon
(**2.20**)

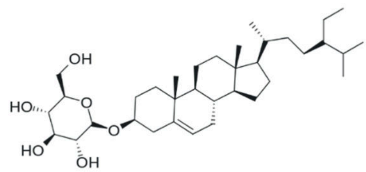
The flavonoids found in the tissue of sweet orange peel are non-iso and non-neo-flavonoids, as glycosides. The widespread flavonoids belong to the flavone group (major components), namely (**2.6**), (**2.8**), (**2.9**), (**2.10**), (**2.11**), (**2.15**), (**2.16**), (**2.17**), (**2.18**), (**2.19**), and (**2.20**). Some belong to the flavanone group, namely (**2.1**), (**2.2**), (**2.3**), (**2.4**), (**2.5**), and (**2.14**). Flavonol, as a derivative of flavonoids, is a minor group, namely (**2.7**), (**2.12**), and (**2.13**).

4.3 Steroids

The isolation of compound contents from methanol extract of sweet orange peels reports the presence of a steroid group characterized as β-sitosterol (**3.1**) and β-sitosterol-3-O-β-D-glucopyranoside (**3.2**) [20].



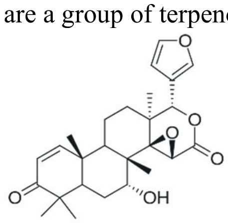
β-sitosterol
(**3.1**)



β-sitosterol-3-O-β-D-glucopyranoside
(**3.2**)

4.4 Terpenoids

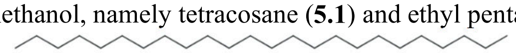
Sweet oranges have a distinctive aroma attributed to the presence of triterpenoid compounds, specifically limonoids (**4.1**), which are a group of terpenoids found in their peel[16].



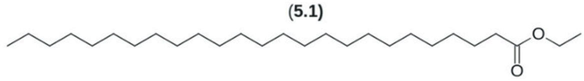
limonoids
(**4.1**)

4.5 Alkanes and Ethyl ester

The groups of alkane and ethyl ester were also identified from sweet orange peel was extracted using hot methanol, namely tetracosane (**5.1**) and ethyl pentacosanoate (**5.2**) [17].



tetracosane
(**5.1**)



ethyl pentacosanoate
(**5.2**)

5 Pharmacological Activities

Pharmacological investigations into the sweet orange peel and the chemistry of its main compound groups, namely essential oils, flavonoids, and other compound categories, have been extensively conducted by researchers. The research findings have shown that these compounds possess beneficial pharmacological properties that align with their traditional medicinal uses long recognized by communities.

5.1 Antioxidant

The presence of flavonoid hydroxylation and flavonoid polymethoxylation in sweet orange peels indicates high antioxidant activity in reducing DPPH radical agents [16]. Decanal, linalool, valencene, and octanal isolated from sweet orange peels exhibited good inhibitory values against DPPH with an IC_{50} value of 66.10 mg/mL [11]. Similar findings were revealed in other research studies, where sweet orange peels extracted using acetone-water solvent were able to inhibit DPPH radicals and showed the ability to reduce ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) [3]. The antioxidant activities of methanol and ethanol extracts from sweet orange peels showed significant free radical scavenging activities, as determined by ABTS with values of 55.8% and 60.7% respectively, and DPPH scavenging activities based on their hydrogen donating abilities at 70% and 80%, where ascorbic acid was used as a control [21,22]. The ethyl acetate fraction exhibited the highest antioxidant activity due to the presence of flavonoid C-glycosylation, flavonoid O-glycosylation, flavonoid polymethoxylation, flavanone O-glycosylation, and phenolic acid esters [23,24].

5.2 Anticancer

The essential oil isolated from sweet orange peel, including decanal, linalool, valencene, and octanal, has shown a significant influence in killing cancer cells. This is demonstrated by their cytotoxic activity against HeLa cells, which are human cervical epithelial cells originating from cervical cancer, with an IC_{50} value of less than 20 μg/mL [11]. The results of isolation of *Citrus sinensis* peel which is a class of polymethoxyflavones showed good activity against lung cancer cells in humans. Nobiletin and 3,5,6,7,8,3',4'-heptamethoxyflavone have an inhibitory ability (IC_{50}) of 50 μM against H1299 cells, while 5-hydroxy-3,7,8,3',4'- pentamethoxyflavone and 5-hydroxy-3,6,7,8,3',4'-hexamethoxyflavone showed an inhibitory value (IC_{50}) of 16.5 μM [25]. Orange peel oil containing a mixture of non-hydroxylated polymethoxyflavones (75.1%) and hydroxylated polymethoxyflavones (5.44%), as well as a mixture solely containing hydroxylated polymethoxyflavones (97.2%), induces apoptosis in MCF-7 breast cancer cells with Minimal Effective Concentrations (ECmin) of 9.25 and 4.62 μg/mL respectively [19]. In in vivo tests using rats fed with a 5% extract of orange peel containing 30% polymethoxyflavones (tangeretin 19.0%, heptamethoxyflavone 15.24%, tetramethoxyflavone 13.6%, nobiletin 12.49%, hexamethoxyflavone 11.06%, and sinensitin 9.16%), tumor development was suppressed [26].

5.3 Antimicrobial

From the conducted research, the oil from sweet orange peel, namely decanal, linalool, valencene, and octanal, has exhibited growth inhibition activity against five microorganism bacteria such as *E. coli, S. aureus, S. cerevisiae, P. citrinum*, and *A. niger* [11]. In the antibacterial activity test using the agar well diffusion method, the oil from sweet orange peel, including limonene, sabinene, β-myrcene, β-pinene, and α-pinene, showed good inhibition against *Staphylococcus aureus* NRRL B-313, Bacillus subtilis NRRL B-354, *Pseudomonas aeruginosa* NRRL B-14781, *E. coli* NRRL B-409, *Clostridium perfringens*, and *Salmonella typhi* YS1646 [9]. By using the disc diffusion method on agar media, it has been reported that the essential oil from orange peel has antibacterial activity against

Escherichia coli ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 21616, *Penicillium chrysogenum* ATCC 10106, *Aspergillus niger* ATCC 16888, as well as a strain of *Saccharomyces cerevisiae* isolated from Distiller's Yeast, with the greatest inhibition observed against *S. aureus* [27].

Based on the research results conducted on the antimicrobial activity test of ethyl acetate fraction from sweet orange fruit peel using the disc diffusion method, it exhibited inhibition activity against *Salmonella typhi, Staphylococcus aureus, epidermidis*, and *Escherichia coli* [28]. Sweet orange oil containing its main compounds decanal, octanal, and linalool obtained through molecular distillation and column chromatography exhibited inhibitory effects on bacterial growth in *E. coli* (MIC 100–25 µg/mL; MBC 200–50 µg/mL), *S. aureus* (MIC 100–50 µg/mL; MBC 200–100 µg/mL), *Saccharomyces cerevisiae* (MIC 100–6.25 µg/mL; MBC 200–25 µg/mL), *Aspergillus niger* (MIC 50 µg/mL; MBC 200–100 µg/mL), and showed no activity against *Penicillium citrinum* [11].

In the antifungal study of sweet orange peel, it has also been stated that there is good inhibitory activity, as reported in [29,30]. Isolated essential oil functions as a good antifungal against *Aspergillus niger*, which is a filamentous fungus causing post-harvest damage to oranges. It has also been reported that ethyl acetate extract from sweet orange peel can inhibit the growth of the fungus *Candida albicans* [28]. Hexane extract from sweet orange peel showed activity against Penicillium digitatum and Cladosporium cucumerinum [31]. Another study indicated that a combination of oils (1:1) from *C. maxima* Burm and *C. sinensis* obtained by hydrodistillation resulted in 100% inhibition of mycelium growth of *Aspergillus fumigatus, A. terreus, Alternaria alternata* at 750 ppm [32]. Polymethoxy flavones obtained from *C. sinensis* peel extract (flavon-7-O-[6-acyl]-glucoside, tetramethyl-O-scutellarein, nobiletin, natsudaidai, tangeretin, heptamethoxyflavone) showed inhibitory activity against the growth of *Aspergillus niger* [33]. In practical applications, the addition of orange peel powder to wheat flour can extend cakes self life due to its high antioxidant activity [34].

5.4 Antiinflamation and antiosteoporotic

Reportedly, essential oil from sweet orange peel has shown anti-inflammatory activity in egg albumin-induced rat edema [35]. In vivo analysis of ethanol extract of C. sinensis peel (5 mg/kg) in ovariectomized rats showed an increase in trabecular bone mineral content, compacted tibial bone mineral, and increased levels of phosphorus and calcium, thereby preventing and reducing bone resorption. [36].

6 Conclusion

With the increasing public interest in a healthy lifestyle and the rise in consumption of functional foods, harnessing the potential of sweet orange fruit peel presents a relevant solution. The compounds present in sweet orange fruit peel, such as essential oil, flavonoid groups, steroids, and terpenoids, have demonstrated good pharmacological activities as antioxidants, anticancer agents, and antimicrobials, as well as anti-inflammatory and anti-osteoporosis agents. As a result, sweet orange fruit peel can be utilized as a component of herbal medicine and is believed to have fewer harmful effects compared to synthetic drugs. Both the powder and extract of sweet orange fruit peel can be developed as food additives to extend shelf life due to their antimicrobial activity. Their antioxidant capabilities can be applied as a sunscreen. The potential as an anticancer agent could offer an affordable herbal treatment alternative, given that current chemotherapy treatments for cancer are very expensive and have adverse effects on the body.

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