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Antioxidant Activity from Various Extracts of Sweet Orange Peel (Citrus Sinensis L.): A Review

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ABSTRACT: Free radicals are molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals. It is charged, highly reactive, and short-lived. High levels of free radicals in the body are indicated by low levels of antioxidants. If the number of free radicals exceeds the number of antioxidants in the body, it will attack the lipid, protein, or DNA components causing oxidative stress. Antioxidants play an important role in preventing the formation of free radicals. The bioactive compounds from citrus peel byproducts are potentially important for reducing risk factors for diseases such as diabetes, neurodegenerative disease, cardiovascular disease (CVD), cancer, cataracts, asthma, arthritis, burns, colitis, ischemic and post-ischemic pathologies. The compounds acting as antioxidants include the enzyme glutathione, albumin, vitamin C, vitamin E, carotenoids, and flavonoids. The review results reported that the solvent affects antioxidant activity. Acetone solvent produces the highest antioxidant activity. Meanwhile, the best solvent obtained in the extraction method with sox is methanol. However, this is certainly also supported by several methods of determining antioxidants such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azinobis-3- ethylbenzothiazole-6-sulfonic acid (ABTS), Ferrous Reducing Antioxidant Power. (FRAP), Cupric Reducing Antioxidant Capacity (CUPRAC), Total Radical-Trapping Antioxidant Potential (TRAP), Oxygen Radical Absorbance Capacity (ORAC), Superoxide Anion Radical Scavenging (SARS), and Cellular Antioxidant Activity (CAA).

Keywords: Free radical, Antioxidant, Citrus sinensis L peel.

I. INTRODUCTION

Free radicals are molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals. Free radicals are uncharged, highly reactive, and short-lived. [1] Free radicals are generally divided into two, namely: Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). The ROS and RNS collectively form all radical and non-radical (oxidant) identities.[1] [2] High levels of free radicals in the body are indicated by low levels of antioxidants. If the number of free radicals exceeds the antioxidant concentration in the body, it will attack the lipid, protein, or DNA components that cause oxidative stress in the form of diseases such as various types of diabetes, neurodegenerative diseases, cardiovascular disease (CVD), cancer, cataracts, asthma, arthritis, burns, colitis, ischemic and post-ischemic pathologies.[3] [4] However, free radicals in certain amounts are beneficial for the body to fight inflammation, kill bacteria, control the smooth muscle that regulates the functioning of internal organs and blood vessels. [5]

Substances that can remove ROS and their derivatives (RNS, or reactive sulfur species, RSS) directly or indirectly, and act as regulators of antioxidant defenses or inhibitors of the reactive species productionare called antioxidants.[6] Antioxidants play an important role in preventing the formation of free radicals. Antioxidants are divided into 2, namely: enzymatic and non-enzymatic antioxidants.[3]

Antioxidants can be classified into three lines of defense according to their mechanism of action; 1) preventing the formation of new free radicals including enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX); metal-binding proteins such as ferritin and ceruloplasmin and minerals such as Se, Cu, and Zn; 2) scavenging free radicals and preventing oxidative chain reactions including the enzymes glutathione, albumin, vitamins C and E, carotenoids, and flavonoids; 3) repairing the damage caused by free radicals to become biomolecules, such as lipases, proteases, DNA repair enzymes, transferases, and methionine-sulfoxidereductase. [7] Antioxidants can be found in vegetables and fruits. One of the fruits very well-known and widely discussed as an antioxidant is a sweet orange.

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The most widely used method of determining antioxidants in vitro is 2,2-diphenyl-1-picrylhydrazyl (DPPH). DPPH is a stable free radical due to the delocalization of spare electrons throughout the molecule. Delocalization in the DPPH molecule is determinedby the occurrence of a purple color, with an absorbance band at a maximum wavelength of about 520 nm. When DPPH reacts with a hydrogen donor, it forms a reduced (molecular) form accompanied by a loss of purple color. Therefore, the decrease in absorbance depends linearly on the antioxidant concentration. Besides, several other methods can be used to determine antioxidant activity including 2,2-diphenyl-1-picrylhydrazyl (DPPH), azinobis-3-ethylbenzothiazole-6-sulfonic acid (ABTS), Ferrous Reducing Antioxidant Power (FRAP), Cupric Reducing Antioxidant Capacity (CUPRAC), Total Radical-Trapping Antioxidant Potential (TRAP), Oxygen Radical Absorbance Capacity (ORAC), Superoxide Anion Radical Scavenging (SARS), and Cellular Antioxidant Activity (CAA). [8] [9]

Sweet orange or Citrussinensis L. is a genus of Citrus from the Family Rutaceae. Oranges are the most widely produced crop in the world.[10]Citrus fruit production of the world in the last decades of the 20th century increases in growth. Annual citrus production is estimated at 105 million tons. [11] The role of citrus fruit in providing nutritional and medicinal value has been known since ancient times, well known for its refreshing properties, quenching power, and providing adequate vitamin C.[12]

Figure 1. Citrus sinensis L.[13]

Oranges have many benefits starting from the pulp, seeds, leaves, and skin of the fruit. The peels of citrus fruits are being studied a lot lately. This is because of orange peel as a by-product that has nutraceutic potential and can offer nutritional dietary supplements at low cost.[14]Also, it is because of its chemical compounds content.

The nutritional content of orange peels includes sugar, protein, vitamins A, C, and minerals. [15-16] Also, orange peel is also reported to contain non-nutritional content called secondary metabolites such: flavonoids (neohesperidin, hesperidin, naringin, nobiletin, narirutin, didymin, sinensetin, eriocitrin, 3 ', 4', 5, 5 '6,7, -hexamethoxyflavone, and tangeretin), alkaloids, terpenoids, tannins, flavonoids, saponins, cardiac glycosides, steroids [15-18]. These compounds have a strong potential for use in the production of drugs or dietary supplements.

Orange peels were reported able to overcome diseases caused by bacteria, viruses, parasites, and fungi. It also has the potential as antibacterial, anti-arteriosclerotic, anti-inflammatory, anti-obesity activity.[19] Another benefit is that it acts as an anti-diabetic, anti-hypercholesterolemic[20], as a hepatoprotective[21], antithrombolytic[22], as an anticancer agent [23], and can overcome the side effects of the cancer drug cyclophosphamide [24]. Most of these effects correlate with antioxidants. This review will discuss the antioxidant activity of orange peels with various solvents.

II. METHODS

Data collections

The preparation of this review article was carried out using literature study techniques from various sources in the form of official books and international articles from the last 10 years (2010 - 2020). The main reference search used in this review article is through trusted webs such as Researchgate, Google Scholar, NCBI, Sciendirect, and other reliable journals.

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Antioxidant ofCitrus sinensis L.

Table1. Antioxidant activity from various extracts of sweet orange

No	Extraction method	Solvent	Test method	IC_{50} value	Ref
1.	Maceration	Methanol/water Ethanol/water Acetone/water	DPPH FRAP ORAC	8.35 to 18.20 mg TE/g 95.00 to 296.61 mmol Fe(II)/g 0.31 to 0.92 mol TE/g	[25]
2.	Maceration	Acetone Ethyl acetate	DPPH ABTS FRAP Lipid Peroxidation	1.7 mg/mL 0.31 mg/mL 8.9 mg/mL 147.9 mg/ mL	[11]
3.	Maceration	Ethanol Chloroform Water	SARS	E: 5% C: 7.25% A: 5%	[26]
4.	Maceration	Ethanol Methanol Acetone	DPPH TRAP ORAC CAA Komet Assay	A : 781.9 µg/mL A: 340.2 µg/mL A : 5.65 µg/mL A : 71.1 µg/mL	[27]
5.	Not mentioned	Methanol Ethyl Acetate Hexane	DPPH FRAP CUPRAC	E: 0.4 ± 0.006g M:19.3 ± 0.1mgTE/g M : 16.8 ± 1.3mgTE/g	[28]
6.	Reflux	Water	TPC	A : 2.4 mg/g	[29]
	Soxhletation	Methanol Ethyl acetate Hexane		M : 4.20 mg/g E: 0.070 mg/g H : 0.120 mg/g	
7.	UAE	Ethanol	ORAC	27.08µM TE	[30]
8.	Reflux Percolation	Ethanol Methanol N-Hexane Ethyl acetate	DPPH CUPRAC	A : 17.94 µg/ml M : 1.4 mg/ml H : 22.9 µg/ml E : 11.4 µg/ml	[31]
9.	Soxhletation	Acetone Methanol Hexane Distilled water	DPPH & FRAP	A : 522 mg/g A : 210 mg/g H : 210 mg/g	[32]
10.	Soxhletation	Ethanol Acetone Chloroform Water	FRAP	A : 40% A : 25% C : 24% A : 43%	[33]

Information :
A: Water
C: Chloroform
E: Ethyl Acetate
H: Hexane
M: Methanol

Citrus sinensis L. has many benefits, one of which is as an antioxidant. The level of antioxidant content was influenced by the

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extraction method, the method of determining antioxidants, and the solvent used. Research reports on the extraction of C. sinensis using methanol, ethanol, and acetone solvents containing important phytochemical compounds such as phenolic acids, flavonoids, and organic acids. The highest antioxidant compounds were obtained in extraction with 70%, 50%, and 100% ethanol and acetone solvents. This shows that the addition of water for extraction can increase the antioxidant levels in the acetone and ethanol extracts. However, in the test using methanol as a solvent high levels of antioxidants were obtained in solvents with concentrations of 100%, 70%, and 50% in the FRAP, and ORAC tests. However, different results were found in the DPPH test, namely with a concentration of 50%, 70%, and 100% (Table 1). [25]

The antioxidant activity in plants is mostly due to the presence of phenolic and flavonoid contents. Research reports that the flavonoid content in plants has high antioxidant activity compared to vitamin C and vitamin E. Oboh, et al. 2012 explained that free phenol testing with 80% acetone extract and bound phenol testing with ethyl acetate extract produced a synergistic effect. This means that both free and bound phenols have the same antioxidant activity even with different solvents using the DPPH, ABTS and FRAP methods. The antioxidant activity of orange peel obtained EC50 value at a concentration of 0.31 mg/mL and had the highest activity as a Fe^{2+} metal chelating agent. [11]

Tests used water, ethanol, and chloroform fractions with the Superoxide Anion Radical Scavenging method have been reported. The chloroform fraction had little antioxidant activity, and no activity was found in the ethanol and water solvent fraction. Among the different fractions of orange fruit peel, the ethanol fraction had an activity of 87.5% starting with a chloroform fraction of 60%. Similar superoxide anion radical activity can be found in the dilute and ethanol fraction of orange peels. [26]

Cellular antioxidant activity (CAA) of methanol extract with acetone orange peel (OP) was higher than that of orange peel (OP) ethanol extract. Meanwhile, Celular antioxidant activity (CAA) orange fruit extract (OF) is not influenced by the type of solvent. Orange peel extract (OP) was significantly higher than Celular antioxidant activity (CAA) orange fruit extract (OF). Acetone as the best solvent for the extraction of antioxidant compounds has also been proven in the results of previous studies. Park et al, 2014 reported that extracts using acetone solvent was rich in phenolics and had strong antioxidant activity in all test methods such as; TRAP, ORAC, CAA, and comets except in tests with the DPPH and RSA methods. The comet test has been used to measure the protective effect of polyphenol compounds from food against oxidative DNA damage that occurs through metal chelation, reactive oxygen species (ROS), and capture of reactive nitrogen species (RNS). [27]

Asseefa et al, 2016 conducted a study using methanol, ethyl acetate, and hexane fractions. The results reported that the solvent that produced the highest amount of phenolic and flavonoid content was found in the ethyl acetate, hexane, and methanol fractions. This means that high antioxidant activity is also shown in the ethyl acetate fraction because of the correlation between high phenolic and flavonoid content and antioxidant activity. The results also reported low IC50 values at concentrations <200 mg/mL. The lower the IC50 value, the higher the antioxidant activity was obtained. Phenols and flavonoids can reduce DPPH radicals which are stable either through the hydrogen process or electron donation characterized by a color change from blue to yellow. [28]

However, it is different from the results of the Harapanrasad&Hema research, 2019 which reported the use of water, methanol, ethyl acetate, and hexane as solvents. The high flavonoid content found in the methanol solvent is 4.20 mg/g, the water solvent is 2.4 mg/g and in hexane is 0.120 mg/g. Whereas, in ethyl acetate solvent found the least flavonoid content was 0.070 mg / g. However, several studies have reported the presence of total flavonoids in hexane extract. The results of the research from Ifason et al. (2013) show that there are fewer flavonoids in hexane extract. Based on these results, it can be concluded that the biological activity of citrus species can be caused by their flavonoid content. [29]

The optimum extraction of bioactive citrus peel compounds using the UEA method was in accordance with the maximum test value of ultrasonic power, extraction time, and the percentage of ethanol in water. The conditions obtained were TC concentration of 0.63 mg β-carotene/100 g, vitamin C concentration of 53.78 mg AA/100g, TSP concentration of 105.96 mg GAE/100 g, ORAC 27.08 µM TE and TEAC 3, 97 µM. The results of these studies indicate that UEA can be used as a non-conventional technique for the

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extraction of bioactive compounds, where the solvent is used for extraction without changing the physicochemical parameters of the final sample. [30]

Determination of the EC50 capacity from the CUPRAC method has been investigated. Half the minimum inhibitory concentration of DPPH activity is the sample or standard concentration that can inhibit 50% of CUPRAC activity. The lowest IC50 or EC50 means the highest antioxidant capacity. Samples that have an IC50 or EC50 less than 50 µg/ml are very strong antioxidants, 50-100 µg/ml are strong antioxidants, 101-150 µg/ml are antioxidants, while an IC50 or EC50 greater than 150 are categorized as weak antioxidants. The IC50 value with the DPPH method from the orange peel extract at the ethyl acetate fraction was 11.4 µg/ml, while for the standard ascorbic acid it had an IC50 value at a concentration of 2 µg/ml. These results concluded that ethyl acetate was a strong antioxidant and was followed by several other solvents, namely methanol 1.4 mg/ml, N-hexane 22.9 µg/ml, and ethanol solvent 17.94 µg/ml. To assess the antioxidant capacity of a sample, various methods must be used in parallel because different methods can give different results. [31]

However, the study by Suja et al. 2017 reported different results. The solvents ethanol, water, and chloroform had stronger antioxidant activity. Ascorbic acid was tested using the FRAP method with high reduction power of 46%, 43%, and 40 respectively. The increase in reducing power is directly proportional to the increase in extract concentration, which means that the higher the extract concentration, the higher the reducing power. The difference between these two studies can be caused by the differences in the methods used, namely maceration and soxhlet. This Citrus extract showed an increase in reducing power along with the increase in extract concentration, namely 50, 100, 250, 500 µg/ml. The increase in reduction power is caused by the presence of phytochemical components in the extract which are electron donors and can react with free radicals and can stop the chain reaction of free radicals. [32]

This can be caused by different methods of extraction and testing of antioxidants used. Flavonoids are knownto have antioxidant activity as discussed by Indra et al. 2019 that the intake of flavonoids above 100 mg has antioxidant activity equivalent to 2-3 mg β-carotene, 70- 100 mg vitamin C, 7-10 mg Vitamin E. Also, the higher the flavonoid content in orange peel, the higher the antioxidant activity is. Soxhlet extract using different solvents produces different results. The extract results obtained were found in methanol, water extract, acetone, and hexane solvents. Methanol solvent as the best extract producer is also proven by Gotmare& Jade's research, 2018 and followed by acetone and hexane. [33] [34]

In the process of determining antioxidants using the DPPH method, the highest antioxidant activity was obtained in methanol solvent. Meanwhile, extraction by maceration showed the highest activity in the soxhlet method. However, different results were obtained with the use of the FRAP method where the highest activity was found in the methanol solvent with the soxhlet extraction method. Whereas in maceration extraction, the ability to absorb Fe^{2+} complex compounds is very little, as a result, the antioxidant activity is minimal. [35]

III. CONCLUSION

The antioxidant activity of citrus Sinensis is abundant in its peel. The antioxidant activity in plants can be resulted from their concentration of phenolic and flavonoid content. The higher the phenolic and flavonoid levels, the higher the antioxidant levels are,and vice versa. The levels of these secondary metabolites vary depending on the type of solvent used. From this review, it can be seen that the acetone solvent plays the most part in producing high antioxidant activity. Of course, this is also supported by the methods used such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azinobis-3-ethylbenzothiazole-6-sulfonic acid (ABTS), Ferrous Reducing Antioxidant Power (FRAP), Cupric Reducing Antioxidant Capacity (CUPRAC), Total Radical-Trapping Antioxidant Potential (TRAP), Oxygen Radical Absorbance Capacity (ORAC), Superoxide Anion Radical Scavenging (SARS), and Cellular Antioxidant Activity (CAA).

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