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Update Review: Comparison of the Use of Extraction Solvents Microwave-Assisted Extraction Method on the Resveratrol Content from Melinjo and its Pharmacological Activity

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Abstract: Resveratrol is one of the active compounds in *Gnetum gnemon L*. In traditional medicine, *G. gnemon* treats arthritis, bronchitis, anemia, asthma, cures eye diseases, and improves urination. The phytochemicals contained in *G. gnemon* are flavonoids, phenolics, tannins, and terpenoids. This review aims to compare the solvent used in the microwave-assisted extraction method on the Resveratrol content from melinjo and its pharmacological activity. This article was written by reviewing scientific articles from 2014-2023 about comparing ionic liquid solvents and organic solvents in Microwave-Assisted Extraction on the Resveratrol content in melinjo and its pharmacological activity. Through review articles, it is known that resveratrol is mostly extracted from the seeds. Extraction using Microwave-Assisted Extraction with ionic liquid solvents produces higher levels of resveratrol than organic solvents. *Gnetum gnemon L.* also has several pharmacological activities such as antioxidant, antimicrobial, antibacterial, antihypertensive, anti-hypercholesterolemic, anti-hyperuricemic, antidiabetic, anticancer, bone healing, tyrosinase inhibition, anti-obesity, and antistress from the seeds and skin. The pharmacological activity influenced by the metabolite extraction method, such as metabolites that can be degraded by heat, can be avoided with the MAE method. Polarity, solubility, dimers, and binding energy of the metabolites, such as resveratrol, also had an impact on the pharmacological activity.

Keywords: *Gnetum gnemon L.*; melinjo; microwave-assisted extraction; resveratrol; extraction.

1. Introduction

Gnetaceae is a family of Gymnosperms with a genus, namely the Gnetum, and the order Gnetales. The genus Gnetum consists of 50 species widely distributed worldwide, such as in Asia, Central America, South America, and West Africa. The diversity of *Gnetum* species is most abundant in tropical and subtropical Asia, including 19 species of *Gnetum*. One

Indonesian species is *Gnetum gnemon L.*, known as melinjo, while other species found in Asia consist of 17 species [1,2].

G. gnemon. can grow wild or is deliberately planted, for example, in gardens, yards, or on the sidelines of residential areas. *G. gnemon* is usually used by people to make food such as sour vegetables and chips. Apart from that, it can also be used as an ornamental plant. *Gnetum* has the morphology of a tree or shrub: branching, gray bark, sharp leaf tips, and oval shape, and each fruit has one seed [3, 4].

In traditional medicine, *G. gnemon* treats arthritis, bronchitis, anemia, asthma, cures eye diseases, and sheds urine [5]. The leaves and fruit are edible. The pharmacological activity of G. gnemon is antioxidant, antimicrobial, anti-inflammatory, anti-obesity, anticoagulant, anticancer, antiplasmodial, hyperuricemia, HMG-CoA reductase, and inhibition of the enzyme tyrosinase [5-7].

Each part of G. gnemon contains various phytochemicals [4]. The Resveratrol compound is classified as a stilbenoid phenolic compound. Stilbenoid compounds are active compounds from *G. gnemon* [8,9].

An effective extraction method is needed to obtain resveratrol, the active compound of melinjo. Microwave-assisted extraction is a new method that uses less solvent and has a shorter extraction time. In previous research, the microwave extraction method has been effective in obtaining the phenol compound from plants [10].

Compared to conventional solid-liquid extraction, MAE is more effective and efficient [11]. This review aims to provide an updated review to compare the use of extraction solvents (ionic liquid solvents and organic solvents) in microwave-assisted extraction methods on the Resveratrol content from melinjo and its pharmacological activity.

2. Materials and Methods

This article was written by collecting and reviewing scientific articles that compare the use of extraction solvents in microwave-assisted extraction methods to the Resveratrol content from melinjo and its pharmacological activity. The article has been published in the last 10 years, including a minimum of 15 articles in the last 2 years. Articles presented in Google Scholar, Science Direct, Springer, PubMed, and Elsevier also have a DOI.

3. Results and Discussion

3.1. Resveratrol.

The phytochemical content of *G. gnemon.* can be found in the skin, seeds, leaves, fruit, stems, flowers, and roots. The levels of compounds in plants vary depending on the climate, varieties, and development conditions [4]. The phytochemical content of melinjo *(G. gnemon.)* can be seen in Table 1.

Table 1. Phytochemical Content of Melinjo *(G. gnemon.)*

Plant	Plant Section	Compound	Reference
Melinjo	Leave	Flavonoids, terpenoids, tannins	[5]
	Twigs	Flavonoids, terpenoids, tannins	
	Seed	Resveratrol, Gnetin C, gnetin L, Isorhapontigenin, Gnemonosides A, Gnemonosides C, and Gnemonosides D	[9]
	Skin	Tocopherol, polyphenols, and ascorbic acid	[12]

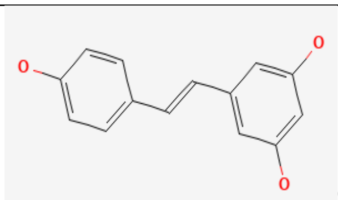
Several studies have revealed that the leaves and twigs contain flavonoids, terpenoids, and tannins [5]. The seeds contain the compounds Resveratrol, Gnetin C, gnetin L, Isorhapontigenin, Gnemonosides A, Gnemonosides C, and Gnemonosides D [9]. The seed coat contains tocopherols, polyphenols, and ascorbic acid [12]. In plants, resveratrol is found mostly in seeds and skin [13].

The bioactive compound of *G. gnemon*is is resveratrol. Resveratrol is classified as a stilbenoid, a phenolic compound. The Resveratrol compound is an active compound from *G. gnemon*. Resveratrol can be isolated from *G. gnemon* in the skin or seeds. Resveratrol can be a monomer or an oligomer. The monomers and oligomers of resveratrol are trans-resveratrol, gnetin C, gnetin E, gnetin L, gnemonoside A, gnemonoside C, and gnemonoside D. In addition, resveratrol can be found free in the form of an aglycone or conjugated as a glucoside [8,9].

The Resveratrol compound has a core structure: two aromatic rings attached to a propane chain to form a C6-C2-C6 arrangement as a monomer and oligomer. Resveratrol is synthesized via the phenylpropanoid pathway. Resveratrol biosynthesis in the phenylpropanoid pathway has amino acid precursors, including phenylalanine and tyrosine [8,14]. Resveratrol consists of changeable cis and trans isomers. However, the trans isomer has stronger pharmacological activity than the cis isomer because its steric hindrance is lower [7,15]. Resveratrol has a C-C double bond, which makes resveratrol sensitive to heat and light, so it tends to oxidize easily [16].

Resveratrol can be stable at acidic pH, around pH 2-7, because the degradation is slow, while resveratrol is unstable at alkaline pH, around pH 8-10, because it can be degraded more quickly. Also, resveratrol is unstable at high temperatures and light, and the solubility is high in alcohol and PEG 400. These physicochemical properties can influence therapeutic effects, storage conditions, and formulation development. Resveratrol has high solubility and permeability because drug permeation can pass through the oil phase, so that drug molecules can dissolve in the oil phase [17-19]. Resveratrol has the molecular formula $C_{14}H_{12}O_3$, molecular weight 228.24 g/mol, PubChem CID 445154 (National Center for Biotechnology Information) [20]. The physicochemical properties of resveratrol can be seen in Table 2.

Table 2. Physicochemical properties of resveratrol.

Resveratrol	
Synonyms	trans-Resveratrol; 3,5,4'-Trihydroxystilbene
Structure	
Molecular formula	 $C_{14}H_{12}O_3$
Molecular Weight	228.24 g/mol
PubChem CID	445154

3.2. Extraction.

Resveratrol is a bioactive compound from melinjo. Resveratrol can be extracted from the skin or seeds. It can be useful for therapeutic purposes by having various pharmacological activities such as antioxidant, antimicrobial, antibacterial, antihypertensive, anti-hypercholesterolemic, anti-hyperuricemic, antidiabetic, and anticancer. The choice of extraction method is very important for extracting phytochemical compounds in plants.

Extraction methods using conventional and non-conventional extraction methods, and the type of solvent, can affect the quality of the extract results. Conventional extraction with organic solvents has many weaknesses. Various factors influence it, so non-conventional extraction methods can be used as alternative methods for better extraction of phytochemical compounds, which have many advantages. Non-conventional extraction methods consist of Microwave-Assisted Extraction (MAE), Supercritical Fluid Extraction (SFE), Ultrasonic-Assisted Extraction (UAE), Subcritical Water Extraction (SWE), Enzyme-Assisted Extraction (EAE), Pressurized Fluid Extraction (PFE), and Pulsed Electric Field-Assisted Extraction (PEF), while conventional extraction methods consist of Soxhlet, reflux, maceration, percolation, and hydrodistillation. The challenges in compound extraction can be influenced by various factors, such as the ratio of sample to solvent. If the solvent ratio is higher than the sample, then it will take a long time to concentrate the extract; the choice of solvent is also very important (polarity, solvent safety, solubility, and selectivity), it will affect the yield of the extract; the particle size of the sample must be considered because if the particle size is too fine, it can cause excessive absorption of the active substance and difficulties in the filtration process; the extraction temperature must be considered because if the temperature is too high, it can cause the degradation of thermolabile compounds; extraction time must also be considered because the longer the extraction time can increase the extraction efficiency of active compounds, however, when solute equilibrium has been reached, the extraction time has an effect [21-24]. Extraction with organic solvents can be done using organic solvents based on the polarity of the solvent, which includes non-polar, semipolar, and polar solvents [21].

The most widely used unconventional extraction method is microwave-assisted extraction (MAE). MAE is a method used to extract bioactive compounds from plants using microwaves. Microwaves produce heat by interacting with compounds in the plant matrix. Microwave-assisted extraction has many advantages, such as higher energy efficiency, faster extraction time, and less solvent usage. The Resveratrol compound from *G. gnemon* can be extracted using Microwave Assisted Extraction [25, 26]. Extraction of Melinjo (*G. gnemon*) can be seen in Table 3.

Table 3. Extraction of Melinjo (G. gnemon).

Extraction method	Plant section	Solvent	Yield of Resveratrol compounds	Reference
Microwave-assisted extraction	Seed	Ionic Liquid	0.5243 mg/g	[27]
	Seed	Ethanol	0.25 mg/g	
	Seed	Ionic Liquid	1.34 mg/g	[28]
	Seed	Ethanol	0.035 mg/g	
	Seed	Ionic Liquid (Br)	0.068 mg/g	[29]
	Seed	Ionic Liquid (Cl)	0.059 mg/g	
	Seed	Ionic Liquid (BF_4)	0.038 mg/g	
	Seed	Ionic Liquid	0.0749 mg/g	[30]

Rachmawati *et al*. conducted research to compare the microwave-assisted extraction method using ethanol and ionic liquid solvent on Resveratrol levels from melinjo seeds. The use of the microwave-assisted extraction method with ionic liquid, with a short extraction time and low power strength, provides the highest Resveratrol content value of 0.5243 mg/g compared to the microwave-assisted extraction method with ethanol solvent (0.25 mg/g). The extraction solvent, time, and power influence the compound levels [27]. Ayuningtyas *et al*. conducted research on the development of a microwave-assisted extraction method with ionic liquid as a solvent on Resveratrol levels. The microwave-assisted extraction method with ionic liquid, with short extraction time and low power, provides a higher Resveratrol content value of 1.34 mg/g than the microwave-assisted extraction method with ethanol solvent of 0.035 mg/g [28]. Arrahman *et al*. conducted research to compare the use of a microwave-assisted extraction method with three ionic liquid solvents, Br, Cl, and BF4, on Resveratrol levels from melinjo seeds. Br used the ionic liquid to give the highest Resveratrol levels of 0.068 mg/g compared to liquid ionic Cl (0.059 mg/g) and BF4 (0.038 mg/g) [29]. Arrahman *et al*. researched melinjo seed extract to test the inhibitory activity of 1-butyl-3-methylimidazolium bromide against dipeptidyl peptidase-4. The extraction of melinjo seeds using a microwave-assisted extraction method with a ratio of solvent to sample and a short extraction time gave the highest Resveratrol content value of 0.0749 mg/g [30].

The results of several studies have been compared with the results of Resveratrol content extracted using microwave-assisted extraction methods using ionic liquid and ethanol solvents. The results of the highest Resveratrol content were carried out using a microwave-assisted extraction method with ionic liquid. The extraction solvent, extraction time, and power strength can influence the extracted Resveratrol compound. The use of ionic liquid as an extraction solvent can extract Resveratrol compounds at higher levels compared to other organic solvents because this ionic liquid has several advantages, namely environmentally friendly solvent, non-volatile, non-flammable, low toxicity, high ionic conductivity, hydrophobicity, polarity differences, and selectivity. Ionic liquids can be used to separate Resveratrol compounds, purify, and obtain compounds that have added value [23].

3.3. Pharmacological activity.

3.3.1. Antioxidant activity.

Sukohar *et al*. tested the antioxidant activity of three fractions of melinjo seed using the DPPH method. Of the three fractions, the ethyl acetate fraction had the highest antioxidant activity of 68.40 ± 1.9 μg/mL [31]. Sari *et al*. tested the antioxidant activity of the ethanol extract of melinjo seeds and skin based on variations in seed color using the nitric oxide and FRAP methods. Green melinjo seed extract using the nitric oxide method provides the highest antioxidant activity of 43.80%, while red skin extract has no antioxidant activity. Meanwhile, the antioxidant activity test using the FRAP method for melinjo bark extract provided the strongest activity, namely in the range of 197.65%239.88%, compared to gnetum seed extract in all color variations [12].

Noviyanti *et al*. tested antioxidant activity on the effect of melinjo seed germination during the 0-21 day period using the ABTS, DPPH, O_2, and OH methods. Antioxidant activity of melinjo seed with a germination period of more than 14 days provides higher antioxidant activity [32]. Saraswaty *et al*. tested the antioxidant activity of the coarse shell fraction of melinjo seeds using porous adsorptive resin. The antioxidant activity of the melinjo coarse shell seed fraction increased 3-7x with an efficient adsorption contact time of 30 minutes [33].

Siswoyo *et al*. tested the antioxidant activity of fermented melinjo flour. Fermented melinjo flour has antioxidant activity, so it can be used as a nutraceutical [34]. Savitri *et al*. tested the antioxidant activity of the ethyl acetate fraction of melinjo seeds using the DPPH method. The ethyl acetate fraction of melinjo seeds has an antioxidant activity of 175.8 g/ml [35]. The condition of the samples that were used for the extraction and determination method affected the results of the antioxidant activity of resveratrol. Resveratrol was known to be well soluble in fat and low solubility in water. Studies by Rachmawati *et al*. showed that the MAE method had higher extraction yield because materials can be rapidly heated and often processed at lower temperatures; thus, the ideal method for substances that can be degraded by heat, like trans-Resveratrol, that have more antioxidant activity [27].

3.3.2. Antimicrobial activity.

Handayani *et al*. tested the antimicrobial activity of a bar soap preparation made from melinjo bark extract. The melinjo bark extract bar soap formula has antimicrobial activity because it can reduce the growth of several bacteria [36]. Dayoh *et al*. tested the antibacterial activity of melinjo extract against S. aureus bacteria. The extract has a minimum inhibitory concentration of 640 mg/ml [37]. The antimicrobial activity of resveratrol is limited by its polarity.

3.3.3. Cytotoxic activity.

Sukohar *et al*. tested the cytotoxic activity of three melinjo seed fractions against HeLa cells. The ethyl acetate fraction had a cytotoxic activity of 45.27 μg/mL [31]. Savitri *et al*. tested the cytotoxic activity of the ethyl acetate fraction of melinjo seeds against HeLa cancer cells. The fraction had a cytotoxic effect of 21.69 g/ml [35]. Fatmawati *et al*. tested the cytotoxic activity of melinjo seed fractions against cervical cancer cells. The melinjo fraction provided cytotoxic activity of 939.723 μg/mL [38]. Indrayudha *et al*. tested the cytotoxic activity of melinjo seed protein fractions on breast cancer cells. Melinjo seed protein fraction had a cytotoxic activity of 127.62 g/mL [39]. The cytotoxic activity of melinjo seed is affected by other metabolites extracted during the procedure. Metabolites such as polar flavonoids could reduce the cytotoxic activity of the extract. At the same time, extracts with higher resveratrol had more cytotoxic activity [31].

3.3.4. Antihypertensive activity.

Noviyanti *et al*. tested the antihypertensive activity of melinjo seed protein on the effect of the germination process. At the beginning of germination, the inhibitory power of ACE-I with IC_{50} was 13.23 μg/mL, but in the following period, it increased until day 21 at 1.14 μg/mL [32]. Triputra and Yanuar tested the antihypertensive activity of 17 compounds isolated from melinjo against the inhibition of Angiotensin in silico. Of all the isolated compounds, only gnetin C, the dimer of resveratrol, and gnemonol K had the highest ACE inhibitory activity [40]. Mun'im *et al*. tested the antihypertensive activity of melinjo seed extract against ACE inhibition and its molecular docking. Ethyl acetate extract provided the highest ACE inhibition of 9.77×10-8 μg/mL [41]. Uson-Lopez *et al*. tested the antihypertensive activity of melinjo seed extract in pregnant rats fed fructose. Giving melinjo seed extract to pregnant female rats can increase vasodilation and reduce high blood pressure [42].

3.3.5. Antihypercholesterolemic activity.

Hafidz *et al*. tested the antihypercholesterolemia activity of five melinjo seed extracts. Dichloromethane seed extract provided the highest inhibitory activity of 64.78% compared to the activity of methanol extract, ethyl acetate extract, water extract, and n-hexane extract of melinjo [43]. Syahdi *et al*. conducted antihypercholesterolemia activity testing to determine the effect of gamma ray irradiation, inhibition of HMG-CoA reductase, and dipeptidyl peptidase-4 from melinjo seeds on Resveratrol content. Ethanol extract of melinjo seeds irradiated at 5.0

kGy gave the highest yield of 0.18 ± 0.004 mg/g [44]. The higher the Resveratrol content in the extract, the higher the inhibition of HMG CoA reductase produced.

3.3.6. Antihyperuricemia activity.

Fadhiilah *et al*. tested the anti-hyperuricemia activity of melinjo seed extract on glutathione levels in mice. Melinjo seed extract can increase glutathione levels in group P1 by 1.55 µg/ml, group P2 by 1.73 µg/ml, and group P3 by 1.88 µg/ml [45]. Rayhan *et al*. tested the anti-hyperuricemic activity of melinjo seed extract in mice. Melinjo extract given to mice at different doses can reduce uric acid levels. Melinjo extract at low doses can reduce uric acid by 56%, while high doses can reduce uric acid by 65% [46]. Tamura *et al*. tested the anti-hyperuricemia activity of melinjo seed extract in rats induced by oxonic acid. Melinjo seed extract can reduce uric acid by increasing ABCG2 protein expression in ileal feces [47]. Kishi *et al*. tested the anti-hyperuricemic activity of melinjo seed extract in reducing uric acid. High doses of melinjo seed extract can reduce serum uric acid levels, the activity influenced by the trans-resveratrol content [48].

3.3.7. Antidiabetic activity.

Rosni *et al*. tested the antidiabetic activity of melinjo seed extract in mice. Giving high doses of melinjo seed extract can reduce glucose levels and increase insulin levels [49]. Supriyadi *et al*. tested the antidiabetic activity of melinjo seed protein hydrolyzate at the seed maturity level. Green melinjo seed hydrolyzate is more effective in providing α-amylase inhibitory activity and α-glucosidase inhibition than red melinjo seed hydrolyzate and yellow melinjo seed hydrolyzate, caused by variation of metabolites in different stages of melinjo seeds [50].

3.3.8. Anticancer activity.

Arifin *et al*. tested the anticancer ethanol fraction of melinjo seeds against colon cancer cells. The ethanol fraction of melinjo seeds has cytotoxic activity of 681 µg/mL against colon cancer cells [51]. Romadhona *et al*. conducted research related to molecular docking studies on the binding affinity of Gnetin C and trans-resveratrol from melinjo seeds to inhibit breast cancer cells. Gnetin C and trans-resveratrol compounds from melinjo seeds can bind protein acids, so they have anticancer potential, even though their docking energy is lower than that of natural ligands. The structure of resveratrol determined the bond and thus showed different anticancer activity [52].

3.3.9. Bone healing activity.

Ikeda *et al*. conducted a study comparing the bone-healing effects of melinjo seed extract on periodontitis mice. Resveratrol dimer may provide greater periodontal bone healing due to the influence of nuclear factor erythroid 2-related factor 2 (Nrf2) [53]. Ikeda *et al*. conducted research on the bone-healing effects of melinjo seed extract on murine periodontitis. The rich Resveratrol Melinjo seed extract can provide bone healing in murine periodontitis by reducing local oxidative damage and inhibiting osteoclast formation [54].

3.3.10. Tyrosinase inhibitory activity.

Saraswaty *et al*. tested the tyrosinase inhibitory activity of melinjo seed micro powder and nanopowder. Melinjo seed nanopowder form with a grinding time of 90 minutes provides the highest tyrosinase inhibitory activity, namely around 35.46%. Nanomilling enhanced metabolites such as phenols, including resveratrol, to be released, thus increasing the activity [55].

3.3.11. Anti-obesity activity

Yoneshiro *et al*. tested an anti-obesity test of melinjo seed extract food supplements, which induced the expression of uncoupling proteins in the fat of mice. Melinjo seed extract can induce adipose tissue thermogenesis in mice and also reduce adipose tissue inflammation. These results can be caused by one of the metabolites in the extract, such as resveratrol, which had activity at the molecular level [56]. Oniki *et al*. tested the anti-obesity activity of melinjo seed extract to increase adiponectin multimerization. Melinjo seed extract at a dose of 300 mg/day can increase levels of total multimerization of adiponectin in serum and disulfide A oxidoreductase-like protein in adipose tissue [57].

3.3.12. Antistress activity.

Barua *et al*. tested the antistress activity of melinjo seed ethanol extract in improving the hypothalamic pituitary adrenal axis in rats. Low-dose melinjo seed ethanol extract can improve and increase plasma glucose, cholesterol, ALT, AST, triglyceride, creatine, and kinase levels. Metabolites in the extract played an important role in antistress activity, but the study was limited to phenols and flavonoid metabolites [58,49].

4. Conclusions

G. gnemon, locally known as Melinjo in Indonesia, contains the compound resveratrol, mostly extracted from the seeds. Extraction using Microwave-Assisted Extraction with ionic liquid solvent produces higher levels of resveratrol than organic solvents. *G. gnemon* also has several pharmacological activities such as antioxidant, antimicrobial, antibacterial, antihypertensive, anti-hypercholesterolemic, anti-hyperuricemic, antidiabetic, anticancer, bone healing, tyrosinase inhibition, anti-obesity, and antistress from the seeds and skin of *G. gnemon.* The pharmacological activity is influenced by metabolites that extracted within such as metabolites that can be degraded by heat, which can be avoided with the MAE method. Polarity, solubility, dimers, and binding energy of the metabolites, such as resveratrol, also had an impact on the pharmacological activity.

Author Contributions

Conceptualization, N.A.; validation, N.A, and A.A.Z.; resources, N.A., A.A.Z., F.N.O., and D.A.N.; data curation, N.A., F.N.O.; writing—original draft preparation, N.A., A.A.Z., F.N.O., and D.A.N; writing—review and editing, N.A and F.N.O.; supervision, N.A.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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