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Research development of *Salacca zalacca* skin against metabolic syndrome: A Review

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Abstract

Metabolic syndrome (MetS) is a group of metabolic disorders involving obesity, insulin resistance, dyslipidaemia and hypertension. The pathogenesis of MetS includes contributing factors such as genetics and epigenetics, physical inactivity, pollutant exposure, and high fat-high sugar intake that develop into a variety of interrelated pathomechanisms. There are various approaches to managing the MetS, including development of herbal medicine which is currently trending. One of the potential herbal products is *Salacca zalacca* (SZ) skin. Salak is a native Indonesian fruit that is also grown in the Asia Pacific region, such as Malaysia, Thailand, the Philippines, and others. However, the management of SZ skin is still limited. Thus, we reviewed studies on SZ skin related to MetS. In this review, we found that SZ skin of various cultivars contain saponins, flavonoids, triterpenoids, steroids, and phenols, which are sources of antioxidants. Moreover, an *in vitro* study found that SZ skin extract inhibits the activity of α-glucosidase enzyme, a key glucose breakdown enzyme that plays a role in the development of hyperglycaemia. In vivo studies also observed that SZ skin extract at a dose of 0.4 mg/mL can increase the expression of SIRT-1, BDNF, and SOD in zebrafish exposed to 3% glucose. In alloxan-induced diabetic rat model showed that the administration of SZ skin extract can reduce blood glucose levels. However, studies on SZ skin as anti-hypertensive and anti-hypercholesterol are very limited. Further studies are needed to consider SZ skin as a potential herbal medicine candidate, especially in managing MetS.

Keywords: *Salacca zalacca* skin; Metabolic syndrome; *In vitro*; *In Vivo*; Review

1. Introduction

Metabolic syndrome (MetS) is a group of disorders resulting from metabolic dysregulation, including insulin resistance, dyslipidemia, central obesity, and hypertension. [1]. Alberti et al. in 2009 defined MetS globally as three abnormal findings, including high blood pressure, dyslipidemia (high triglycerides with low high-density lipoprotein cholesterol), high fasting glucose, and central obesity, as proposed by the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute [2]. According to the National Health and Nutrition Examination Survey (NHNES), the prevalence of MetS in adults increased from 25.3% to 34.2% in 2012, with a peak prevalence in the early 21st century in the United States, and decreased gradually due to scientific improvement, early diagnosis, and appropriate treatment of dyslipidemia and hypertension [3, 4]. In Europe and Latin America, approximately a quarter of the general population is reported to have MetS [5, 6]. The incidence of MetS in China has also increased over the past 3 decades [7]. In 2020, 3% of children and 5% of adolescents globally suffer from MetS, especially in children in low-income countries [8]. This suggests that the incidence of obesity and metabolic-related diseases is not related to a nation's income and status.

The pathogenesis of MetS includes several complex mechanisms influenced by genetic factors, physical activity, exposure to pollution, and nutritional intake [9]. Among the established mechanisms, including hypertensive

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conditions, chronic inflammation, hormonal abnormalities, and insulin resistance, play an important role in the incidence of MetS, as shown in **Figure 1.**

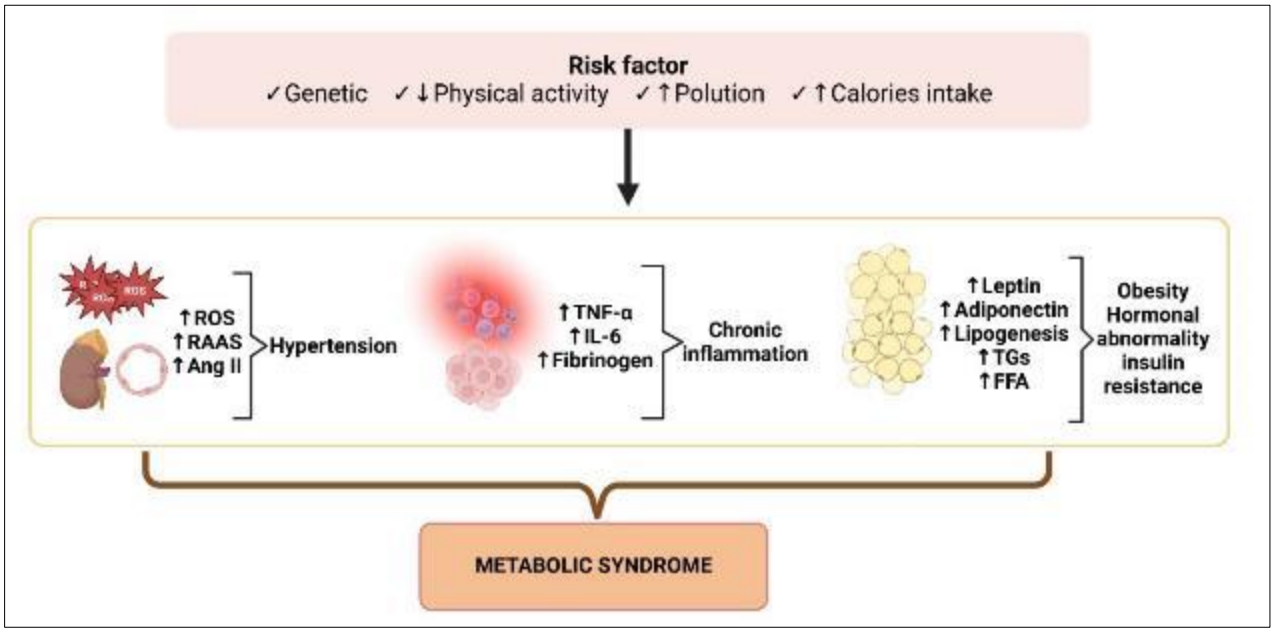

Figure 1 The proposed pathogenesis of MetS

The pathogenesis of MetS involves a variety of different but interrelated mechanisms. Numerous studies have shown concordance between the various mechanisms, with oxidative stress and chronic inflammation being crucial to the development of MetS [10]. Oxidative stress is a condition of imbalance between the oxidative and anti-oxidative systems of cells and tissues resulting in excessive production of oxidative free radicals and reactive oxygen species (ROS). Excessive ROS production can damage cellular proteins, lipids, and nucleic acids, leading to cellular-level dysfunction including loss of energy metabolism, changes in cell signaling and cell cycle control, genetic mutations, changes in cellular transport mechanisms, as well as a decrease in overall biological activity. Oxidative stress also occur in high-fat and high-carbohydrate diets as manifested by increased lipid peroxidation products, protein carbonylation, and decreased antioxidant systems, as well as decreased glutathione (GSH) levels. This develops a pathogenic environment and several chronic diseases, such as obesity, hypertension, atherogenic dyslipidemia, diabetes, cancer, and cardiovascular disease [10, 11].

Hypertension is one of the most common manifestations of metabolic disorders associated with hyperinsulinemia and insulin resistance, which are key factors in the development of MetS. Adipocytes release several factors, including adiponectin, leptin, and resistin, that play a role in blood pressure regulation [12]. In addition, abnormal glucose tolerance in hypertension is a compensatory response against reduced insulin-stimulated glucose uptake by skeletal muscle [13, 14]. Central obesity was also proven to be involved in two-thirds of the developmental factors of insulin resistance derived from adipose tissue [15]. Increasing fat breakdown to free fatty acids (FFAs) affects PI3K activity associated with insulin receptor substrate (IRS-1), leading to decreased GLUT-4 translocation to the surface and thus reduced glucose uptake. Insulin resistance leads to hypertension through the inhibition of insulin and fatty acid-mediated vasoconstriction and plays a role in the release of pro-inflammatory cytokines from adipose tissue and the prothrombotic state [8]. Visceral adipose tissue in central obesity also produces metabolites and biologically active substances, including glycerol, free fatty acids (FFAs), pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), leptin, and resistin, and decreased secretion of adiponectin [16, 17]. Elevated pro-inflammatory cytokines in MetS suggest that chronic inflammation also plays an important role in the development of MetS [18, 19]. In addition, high concentrations of FFAs increase the synthesis of cholesterol and triglyceride (TG) esters and subsequent production of TG-rich very low-density lipoproteins (VLDL). Which in turn activates cholesterol ester transfer protein (CETP), which promotes the transfer of TG from VLDL to HDL, increasing HDL clearance and decreasing its concentration [1].

The treatment of MetS is determined based on clinical findings, physical examination results, and other relevant tests. Early detection and treatment can control MetS. Currently, there is a lot of research related to MetS, especially the development of drugs from natural resources. The development of natural medicine or herbal medicine is one of the

efforts to overcome medical complaints and control the disease. Among the herbal resources utilized is salak (*Salacca zalacca*) skin. Salak (*Salacca zalacca*) is a palm tree that belongs to the Palmae family or *Arecaceae* genus *Salacca*. *Salacca zalacca* is an indigenous plant of South Sumatra and Southwest Java that is spread throughout the entire Indo-Malaysian region, including Thailand, Indonesia, Malaysia, Cambodia, and Southern Myanmar, Vietnam, the Philippines, and China [20, 21]. *Salacca zalacca* has more than 30 cultivars categorized by fruit skin color, fruit size, flavor, and texture [22]. Despite its high abundance in the Asian region, most of the processing of *Salacca zalacca* is centered on its fruit pulp [20, 22]. The hard-textured skin of *Salacca zalacca* (SZ skin) is often not considered for further processing. In Indonesia, people traditionally process SZ skin into tea and coffee because of their antioxidant, anti-inflammatory, anti-diabetic, anti-hypercholesterol, and other benefits [21, 23, 24]. However, research related to SZ skin is still limited. Thus, this study aims to review the development of research on SZ skin related to MetS due to its potential and abundance in nature that should be maximally utilized.

2. Review of literature

We conducted a review study of published articles on *metabolomics, in vitro,* and *in vivo* studies of SZ skin regarding its role in MetS. Research by Kanlayavattanakul et al. reported that salak skin (*S. sedulis*) is known to have various polyphenol contents that act as antioxidants and are proven by 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and ferric-reducing antioxidant power (FRAP) radical scavenging tests to determine the radical scavenging capacity with 50% inhibition concentrations (IC50) of 2.93 µg/mL, 7.93 µg/mL, and 7844.44 µg/mL, respectively [25]. The fourier transform infrared spectroscopy (FTIR) examination of the SZ skin cultivar Bali, Indonesia, showed that the outer and inner extracts of SZ skin observed a strong band at 3225 cm^{-1} attributed to the hydroxyl group, and the band appeared more clearly for the outer SZ skin. The band at 2950 cm^{-1} is characteristic of the CH group, and the C=C and C=O bands are found in the 1590–1458 cm^{1} region. Aromatic groups of type I and II amides appear in the region between 1390 and 1320 cm^{-1}. CO, ester, hydroxyflavone, catechin, and amide type III groups were seen in the 1220-1150 cm^{-1} region, especially in the outer SZ skin, and aliphatic amine functional groups were dominant in the 1000-700 cm^{-1} region. The SZ skin extract showed weak IR bands between 1140 and 1075 cm^{-1} specific for C\N stretching vibrations of aliphatic amines or C\O stretching vibrations of alcohols or phenols. The antioxidant capacity test was also measured by the DPPH free radical scavenging method. Methanol extract of salak fruit extract showed high antioxidant capacity compared to SZ skin extract (SZ core = 82.67 % and SZ shell = 73.13 %) [26].

A study on the SZ skin cultivar Malang, East Java, Indonesia, conducted by gas chromatography-mass spectrometry (GC-MS) reported that the ethanol extract of SZ skin contained proteins [D-(+)-Proline, Leucylproline, and L-Phenylalanine], ferulic acid, phenolics (Phenol, Tyrosol, and Caffeic Acid Phenethyl Ester), flavonoids (Tetramethoxyflavanone, Genistein, Hesperidin, and Keampferol), and glycosides (Salidroside and Asiaticoside). In addition, the expression assay of silent information regulator 1 (SIRT-1), brain-derived neurotrophic factor (BDNF), and superoxide dismutase (SOD) in zebrafish embryos exposed to 3 % glucose reported that exposure to 3% glucose decreased the expression of SIRT-1, and the administration of 0.4 mg/mL SZ skin extract was able to increase the expression of SIRT-1 significantly. Meanwhile, the highest average BDNF expression was found in 3% glucose + 0.4 mg/mL SZ skin extract. The treatment of SZ skin extract can also significantly increase the SOD of zebrafish embryos at a concentration of 0.4 mg/mL [27]. In another study, Husnul et al. reported that ethanol extract of Malang SZ skin significantly reduced the expression of interleukin-1β (IL-1β) and Bcl-2 Associated X-protein (Bax) at a concentration of 0.4 mg/mL and was also able to reduce the expression of Apoptotic Peptidase Activating Factor 1 (Apaf-1) with the most similar results to the negative control at a concentration of 0.4 mg/mL and reduce the expression of IL-1β in embryos aged 3 dpf exposed to high glucose. [28].

The bioactive studies of 4 types of salak skin also reported that SZ skin contains bioactive substances that have antioxidant effects, namely flavonoids, polyphenols, ferulic acid, and tannins, that are sufficiently high. The highest total phenolic content of the extract was obtained from Salak Mawar skin, at 186.15 mg gallic acid equivalent/g extract, while the highest total flavonoid content was obtained from Salak Malacca fruit peel extract at 7.43 mg quercetin equivalent/g extract. [29]. Another study also mentioned that SZ skin extract cultivar Medan, North Sumatra, Indonesia was found to contain phytochemicals in the form of alkaloids, steroids/triterpenoids, flavonoids, and tannins through the modified Fanssworth method [30]. This was also demonstrated by qualitative examination of the ethanol extract of SZ skin from Bogor, West Java, Indonesia, which contained flavonoids, saponins, phenols, tannins, triterpenoids, and alkaloids. Meanwhile, based on the results of targeted screening through liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS), the ethanol extract of SZ skin contains chlorogenic acid at approximately 1.073 mg/g dry weight [31].

Several SZ skin studies have also highlighted its anti-diabetic effects. Research by Saleh et al. reported that in vitro ethanol extract of SZ skin has an anti-hyperglycemic effect through glucosidase enzyme inhibition with an IC50 value of 11.62 ± 0.67 g/mL [23]. An in vitro study of SZ skin extract reported that the highest anti-diabetic activity in the form

of glucosidase enzyme inhibition was found in Salak Manonjaya cultivar(IC50: 17.9 µl/dl) [29]. Another study showed that the SZ skin from Balikpapan can reduce blood glucose levels in diabetic mice at a dose of 210 mg/kgBB with 40.94 % inhibitory activity [32]. In addition, the SZ skin of the Medan cultivar also has anti-hyperglycemic effects at the lowest dose (60 mg/200 gBW) in Wistar rats with alloxan-induced diabetes [30]. The *Rattus norvegicus* alloxan-induced diabetes rat model also showed that SZ skin extract can effectively reduce blood sugar levels with an optimum dose of 600 mg/kgBW [33]. However, the studies on the efficacy of SZ skin as an anti-hypertensive and anti-cholesterol agent are limited and undocumented. The study by Tan et al. reported a comparative test between solvents used in SZ skin extracts. Their study showed that the angiotensin-converting enzyme (ACE) inhibitory activity of distilled water extract of salak skin was better than that of methanol and ethanol extracts, with inhibition percentages of 86.94 ± 1.60 %, 98.76 ± 0.96 %, and 98.96 ± 0.98 %, respectively [34]. In summary, the SZ skin extract showed ACE inhibitory potential, which is in line with one of the pathomechanisms of hypertension.

The existing studies are a promising step forward towards the development of SZ skin as a herbal product for the future. In general, SZ skins have similar contents and effects. Environmental, climatic, and geographical conditions may contribute to the differences in content. More studies related to SZ skin are an important step in considering it as a potential standardised herbal medicine candidate. The abundance of SZ skin in nature and its bioactive content is a national treasure that needs to be utilised to its full potential.

3. Conclusion

Salak or *Salacca zalacca* is an native Indonesian fruit that also grows in the Indo-Pacific region with high abundance in nature. It is a natural resource that needs to be optimally utilised. Utilisation that focuses on the flesh of *Salacca zalacca* fruit increases the volume of *Salacca zalacca* (SZ) skin produced. The SZ skin has been traditionally used to treat medical complaints, but its scientification has not been well documented. Several studies have focused on the antioxidant and anti-hyperglycaemia properties of SZ skin, which are beneficial in managing diabetes and controlling the progression of MetS. However, there has not been much research on the anti-hypertension and anti-cholesterol properties of SZ skin.

Compliance with ethical standards

Disclosure of Conflict of interest

The authors declare that they have no competing interests.

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