

## POTENTIAL BENEFITS OF RESVERATROL DERIVATIVES FOR TREATMENT AND PREVENTION OF METABOLIC SYNDROMES

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### ABSTRACT

Metabolic syndrome refers to risk factors that enhanced the development of cardiovascular disease and diabetes. Resveratrol is a stilbene compound. Various resveratrol derivatives have been isolated and identified from natural product extracts. Those compounds may present in the form of a monomer, dimers, trimers, or even more complex derivatives as the impact of structure modification during biosynthesis. Over the years, resveratrol and its derivatives have been explored on its pharmacological effects. In this paper, we reviewed the potency of several well-characterized resveratrol derivatives isolated from natural product extract for the treatment and prevention of metabolic syndromes. We reveal that resveratrol derivatives can be used for prevention and treatment metabolic syndromes such as obesity, diabetes, hyperuricemia, as well as an inflammatory condition by interfering multiple targets, for example inhibiting several enzymes including xanthine oxidase, lipase,  $\alpha$ -glucosidase, DPP-IV, and angiotensin-converting enzyme, activating PPAR- $\alpha$  and PPAR- $\beta/\delta$ , reducing visceral adipose fat, as well as downregulating GLUT9 and URAT1 ion transporter. The potency of those resveratrol derivatives such as gnetin C (isolated from *Gnetum gnemon* seed) and mulberroside A (isolated from *Morus alba*) seem superior as compared with trans-resveratrol as its parental compound *in vitro* and exhibited positive effect in an animal model. Hence, we suggest natural product extract containing resveratrol derivatives may provide promising prospects as an alternative medicine for treatment and prevention of metabolic syndrome.

**Keywords:** Resveratrol Derivatives, Mulberroside A, Gnetin C, Metabolic Syndrome.

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### INTRODUCTION

According to the American Association of Clinical Endocrinologists (AACE) and World Health Organization (WHO), metabolic syndromes are generally signed by hypertension, high glucose level (type 2 diabetes mellitus), pro-inflammatory state (hyperuricemia), as well as dyslipidemia.<sup>1,2</sup> Lots of epidemiological data demonstrate that daily food intake, physical activity, smoking, family history of diabetes as well as genetic background are remarkably associated with the prevalence of metabolic syndrome. Furthermore, the incidence of metabolic syndrome tends to increase year by year due to the changes in lifestyles.<sup>3-9</sup> Against metabolic syndromes with natural product extract derived compounds appears to be a fascinating strategy because of its low toxicity and has a constructive effect as compared with the chemically synthesized drug.

Resveratrol (3,5,4'-trihydroxytrans-stilbene), is a stilbene compound present in several fruits and vegetables including grapes, peanut, itadori, and melinjo.<sup>10,11</sup> During the last decade, numerous preclinical studies have shown that resveratrol and its derivatives attracted considerable attention because of its potency in the prevention of several ailments including cardiovascular disease, hyperuricemic, diabetes mellitus, as well as aging. Resveratrol and its derivatives are reported reducing blood serum uric acid, blood serum glucose, as well as blood serum cholesterol levels by inhibiting various enzyme activities

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associated with those ailments that are xanthine oxidase,<sup>12</sup> lipase, as well as amylase<sup>13</sup> enzymes *in vitro*. However, those effects have not yet been confirmed in clinical trials using patients, due to the practical boundaries related to the investigation of metabolic syndromes.

In nature, resveratrol is biosynthesized in plants as a response to microbial infection, injury, as well as ultraviolet radiation.<sup>10</sup> The resveratrol derivatives can be found in the form of dimers, trimers, tetramers, and even more complex compounds as the impact of structure modification as well as complexation during biosynthesis.<sup>14-16</sup> However, the biogenesis of these compounds has not been thoroughly understood. It seems that the coupling of regioisomeric modes generates broad resveratrol dimeric skeleton that can undergo various reaction then producing more complex structures.<sup>17</sup>

The investigations that some resveratrol and its derivatives possess pharmacological activities (Fig.-1), including antioxidant<sup>18-20</sup>, antimicrobial,<sup>13</sup> anticancer,<sup>21,22</sup> antiobesity,<sup>23</sup> antiaging,<sup>19,24,25</sup> inhibitor of various enzyme, antihypertension,<sup>12,13</sup> as well as anti-alzheimer disease,<sup>26</sup> have carried out to generate the scientific interest in these resveratrol derivatives. It seems that most of resveratrol derivatives are obtained in small amounts from natural product extracts, and majorly previous investigations have focused on the evaluation of its monomer (trans-resveratrol).<sup>27-31</sup> Hence the pharmacological activities of only several resveratrol derivatives have been well studied. Although several of these compounds are reported having pharmacological effects related to metabolic syndromes, most of them only have tested *in vitro* (Table 1). Hence, it is not surprising that safety assessment as well as pharmacokinetic data of these resveratrol derivatives are lack and scarce.

A lot of investigations have shown the various potential of resveratrol derivatives as an alternative drug to prevent and treat metabolic syndrome, so far there is no systematic review about the potency of those compounds. In this paper, we resume the pharmacological activities of several resveratrol derivatives whose structure can be seen in Fig.-2, for the prevention and treatment of metabolic syndromes associated with obesity, type 2 diabetes mellitus, hyperuricemic, as well as inflammation and propose the action mechanism.

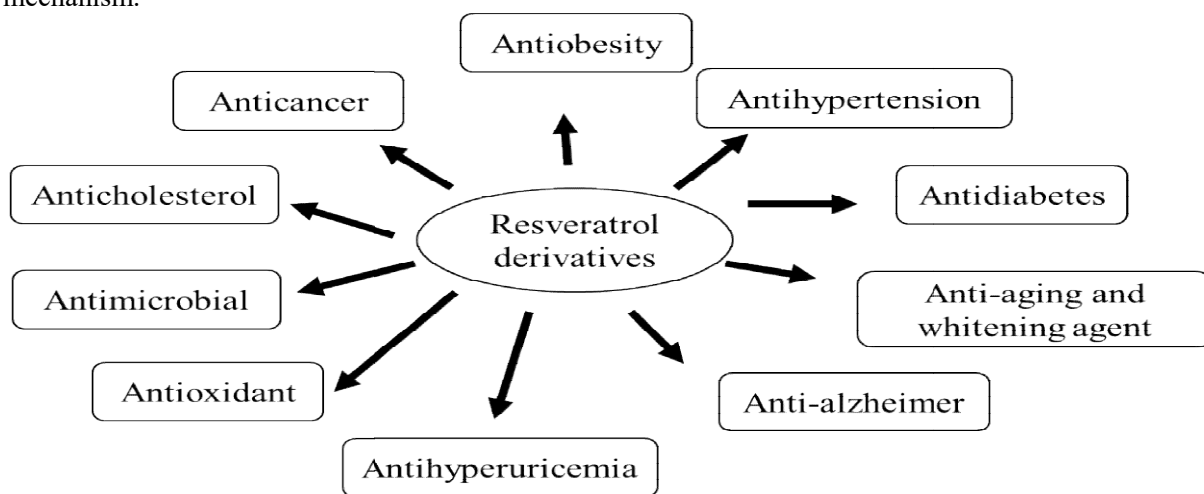


Fig.-1: Pharmacological Activities of Resveratrol Derivatives

Table-1: Naturally Resveratrol Derivatives with Anti-metabolic Syndromes Potential

Resveratrol Derivatives	Source	Mechanism of Action	<i>In vitro/in vivo</i> /Clinical Trial	Reference
Mulberroside A	<i>Morus alba</i>	Downregulating GLUT9 and URAT1; upregulating OAT1, OCT1, OCT2, OCTN1, and OCTN2; suppressing NO and iNOS expression	<i>In vitro, in vivo</i>	32-34
Gnetin C	<i>Gnetum gnemon</i> seed	Inhibiting xanthine oxidase, Lipase and $\alpha$ -amylase enzymes	<i>In vitro, in vivo</i> , clinical trial	12,13,35-38

Gnemonoside D	<i>Gnetum gnemon</i> seed	Inhibiting lipase enzyme	<i>In vitro</i>	13
Gnetin L	<i>Gnetum gnemon</i> seed	Inhibiting lipase enzyme	<i>In vitro</i>	13
Gnetin H	<i>Paeonia lactiflora</i>	Inhibiting $\alpha$ -glucosidase, DPP-IV, and PTP1B enzyme; Suppressing cytokine response involved in the NF- $\kappa$ B pathway.	<i>In vitro</i>	39-41
$\alpha$ -Viniferin	<i>Caragana chamlagu</i> root	Inhibiting LPO activity, COX-2 and iNOS	<i>In vitro</i>	42
Hopeaphenol	<i>Vateria indica</i> Linn stem bark and <i>Ampelocissus indica</i> (L.) rhizome	Inhibiting $\alpha$ -glucosidase enzyme; lowering plasma lipase activity	<i>In vitro, in vivo</i>	43-46,47
Vitisin A	ethanol extracts of <i>Vitis thunbergii</i> var. <i>taiwaniana</i> stem.	Inhibiting $\alpha$ -glucosidase and DPP-IV, ACE enzyme; lowering plasma lipase activities, reducing weight;	<i>In vivo, in vitro</i>	47-49
Vaticanol B	<i>Shorea gibbosa</i> bark.	Reducing visceral adipose fat; Reducing the protein load and maintaining the membrane integrity of the ER.	<i>In vivo, in vitro</i>	50-52
Vaticanol C	<i>Vatica rassak</i> , <i>Shorea roxburghii</i> and <i>Vatica pauciflora</i> .	Activating PPAR- $\alpha$ and PPAR- $\beta/\delta$	<i>In vitro, in vivo</i>	53-55,59,56

### Mulberroside A

Mulberroside A (**1**), is a glycosylated resveratrol monomer that has been isolated from several species of the Moraceae family including *Morus alba* and *Ramulus mori*. Mulberroside A isolated from *Morus alba* root has been evaluated for its anti-hyperlipidemic effects in an animal model.<sup>32,33</sup> Oral administration Mulberroside A at 1 to 5 mg/kg bw significantly reduced blood serum lipids level in induced hyperlipidemic rats.<sup>33</sup> Mulberroside A was reported downregulating mRNA and protein levels of renal glucose transporter 9 (mGLUT9) and urate transporter 1 (mURAT1) in induced hyperuricemic mice. Also, this compound was reported upregulating mRNA and protein levels of renal organic anion transporter 1 (mOAT1) and carnitine transporters (mOCT1, mOCT2, mOCTN1, and mOCTN2),<sup>34</sup> indicating its potential as antihyperuricemic and nephroprotective agent.

There is growing evidence that silent chronic inflammation is one of the key factors in metabolic syndrome and cardiovascular disease.<sup>57</sup> cis-Mulberroside A was reported exhibiting suppressive effect on the NO production and inducible nitric oxide synthase (iNOS) expression in lipopolysaccharide (LPS)-stimulated macrophage, suggesting a strong potency as an anti-inflammatory as well as analgesic agent.<sup>32</sup> Following the results of antihyperuricemic, antihyperlipidemic as well as antiinflammation effect in an animal model, Mulberroside A has considerable therapeutic potential in the prevention of metabolic syndrome and merits for being considered to be tested in clinical trials for cardiovascular therapeutic.

### Gnetin C

Gnetin C (**2**) is a resveratrol dimer that has been isolated from several species of Gnetaceae including melinjo or *Gnetum gnemon*.<sup>13</sup> This compound also can be found in *G. africanum* and *G. schwackeanum*.<sup>35-36</sup> The ethanol extract of melinjo seeds is rich in resveratrol and its derivatives including gnetin C, gnemonoside A (**3**), gnetin L (**4**) as well as other stilbene derivatives. Consumption of melinjo seed extract at 750 mg/day for 8 weeks was well tolerated and decreased blood serum uric acid level in

non-obese males (Japanese) healthy volunteers. As a single compound, gnetin C inhibited 50% ( $IC_{50}$ ) xanthine oxidase (XO) enzyme activity at 133  $\mu\text{g/mL}$ .<sup>12</sup> The potency of gnetin C as XO inhibitor looks superior as suggested by its lower  $IC_{50}$  value compared with its parental compound (trans-resveratrol). Based on the chemical structure, we suggest that in the form of dimer, resveratrol derivative is more active as XO inhibitor.

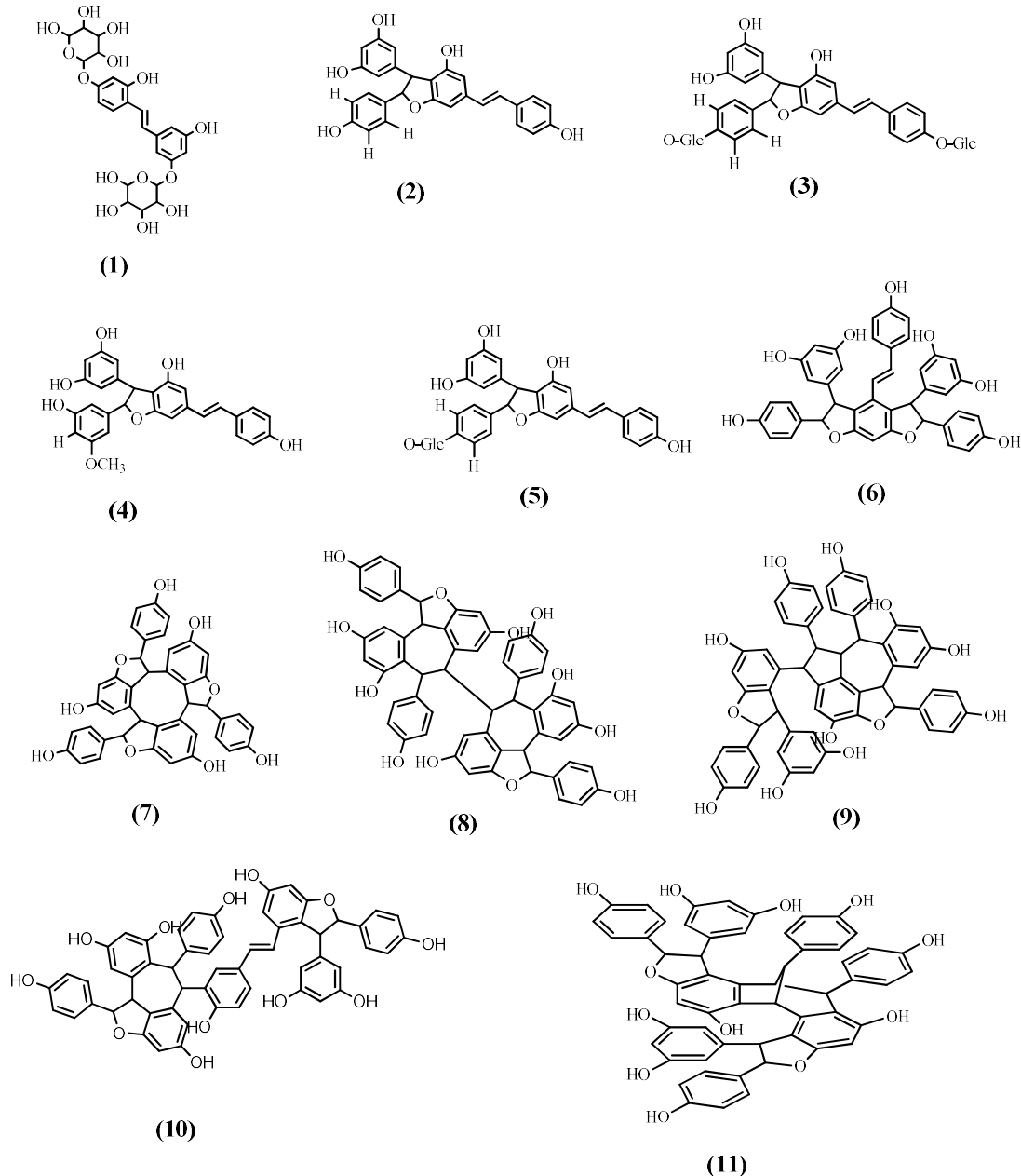


Fig.-2: Chemical Structure of Naturally Resveratrol Derivatives

It seems, that melinjo seed extract is also a potential source of antiobesity and anti-diabetes agents as suggested by the potency of gnetin C, gnetin L and gneunoside C (5) inhibiting the lipase and  $\alpha$ -amylase enzyme.<sup>13</sup> The potency of gnetin C to prevent metabolic syndrome including obesity, hyperuricemic, and cardiovascular disease was emphasized in the clinical trial whose results show that consumption of pure gnetin C at 150 mg/day remarkably decreased the blood serum uric acid, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total adiponectin, and high-molecular-weight adiponectin level.<sup>37</sup>

The pharmacokinetic profile of gnetin C has been studied. A study reported that the mean residence time (MRT) of gnetin C was 36 h and less for trans-resveratrol (MRT of 24 h), and gnetin C was still present in the blood plasma for up to 96 h.<sup>38</sup> Those results were also supported by an investigation reporting higher concentration of gnetin C than trans-resveratrol in blood serum of streptozotocin-induced diabetic mice after oral administration of melinjo seed extract, showing the longer bioavailability of gnetin C than trans-resveratrol.<sup>58</sup> A study also reported that melinjo seed extract was well tolerated up to 1000 mg/kg bw in mice without any sign of adverse effect or toxicity.<sup>59</sup> Hence, we suggest that either gnetin C or melinjo seed extract is safe for being consumed.

In summary, those above data evidence the potential benefits and safety of gnetin C. Thus, natural product extract containing a large amount of gnetin C including melinjo (*Gnetum gnemon*) should be considered for being developed as an alternative medicine for prevention and treatment of metabolic syndrome.<sup>22</sup> However due to the clinical trials only provided data from healthy volunteers, therefore further works are needed to confirm the biological effect in patients with metabolic disorder condition.

### Gnetin H

Gnetin H (6) is a resveratrol trimer isolated from *Paeonia lactiflora*. This compound has been reported possessing anti-diabetes (type 2 diabetes mellitus) properties, as suggested by inhibition of  $\alpha$ -glucosidase, dipeptidyl peptidase-4 (DPP-IV) and protein tyrosine phosphatase 1B (PTP1B) enzyme activity. *Trans* - gnetin H inhibited those enzyme activities greater than that of *cis* form.<sup>39</sup> Also, experiments evidence showed that *cis*- and *trans*-gnetin H suppressed cytokine response in LPS-stimulated THP-1 cells by preventing activation of key signaling molecules, IKK- $\beta$ , I $\kappa$ B  $\alpha$ , and p65, involved in the nuclear factor kappa B (NF- $\kappa$ B) pathway.<sup>40</sup> Thus, despite the potency of gnetin H as an anti-diabetes agent, this compound also exhibits an anti-inflammatory effect.<sup>41</sup> Hence, gnetin H has the potential to prevent and treat metabolic syndrome. However, further studies either in an animal model and clinical trial in healthy individuals or patients should be carried out to warrant this biological activity.

### $\alpha$ -Viniferin

$\alpha$ -Viniferin (7) is trimeric resveratrol isolated from an n-hexane extract of *Caragana chamlagu* root.<sup>60</sup> Pharmacological studies have shown that  $\alpha$ -viniferin inhibited lipid peroxidation (LPO) and inflammatory activity.<sup>42,61</sup> The inflammatory activity of  $\alpha$ -viniferin was suggested by inhibition of cyclooxygenase-2 (COX-2) as well as iNOS activity.<sup>61</sup> Additionally,  $\alpha$ -viniferin also exhibited a powerful anti-inflammatory activity by suppressing ERK-mediated STAT1 activation in interferon- $\gamma$ -stimulated macrophages.<sup>62</sup> Together, those studies reveal that  $\alpha$ -viniferin interacts with several targets associated with inflammatory as well as obesity condition. Suggesting natural product containing large amount of  $\alpha$ -viniferin merits for being considered as alternative medicine for treatment of obesity as well as inflammation. However, due to the lack of *in vivo* investigations as well as the safety assessment of this compound, we suggest performing more *in vivo* experiments to ensure the biological activities.

### Hopeaphenol

Hopeaphenol (8) is a resveratrol tetramer that has been isolated from several species of the Vitaceae, Dipterocarpaceae, Cyperaceae and Fabaceae family.<sup>43-46</sup> Purified Hopeaphenol from acetone extract of *Vateria indica* Linn stem bark and *Ampelocissus indica* (L.) rhizome was reported significantly inhibiting  $\alpha$ -glucosidase enzyme, showing its potential to treat type 2 diabetes mellitus.<sup>46</sup> Surprisingly, in an experiment using animal model, oral administration of hopeaphenol at 25 mg/kg bw did not show a reduction of body weight. However, at the same dose this compound lowered plasma lipase activities.<sup>47</sup> Thus, we expect that the potency of hopeaphenol at a dose of 25 mg/kg bw is less effective to ameliorate obesity and required higher dose. In addition, as suggested the efficacy of this compound tends to associate with enzymes. Likewise, despite the potency of hopeaphenol in prevention of metabolic syndrome, however, those pharmacological data are lack and scarce. We suggest to do further investigations *in vivo* to clarify this biological activity.

### Vaticanol B

Vaticanol B (9) is a resveratrol tetramer that has been isolated from methanol extract of the tree bark of *Shorea gibbosa*.<sup>50</sup> This compound largely found in Dipterocarpaceae family.<sup>55</sup> In an experiment, treatment of

zebrafish with Vaticanol B showed antiobesity activity that was almost similar in potency to that of resveratrol.<sup>51</sup> Vaticanol B was reported reducing the protein load on the endoplasmic reticulum (ER) and maintaining the membrane integrity of the ER.<sup>52</sup> It should be noted that type 2 diabetes mellitus induces oxidative stress as well as ER stress of the endothelium which play major roles in the initiation and progression of cardiovascular clinical manifestations.<sup>63</sup> Hence, the potency of vaticanol B in the regulation of ER stress may reduce the risk of diabetes mellitus complication as well as metabolic syndromes. It seems that the scarce of pharmacokinetic study as well as safety assessment *in vivo* and humans are the main limitations of applying the therapeutic potential of this compound.

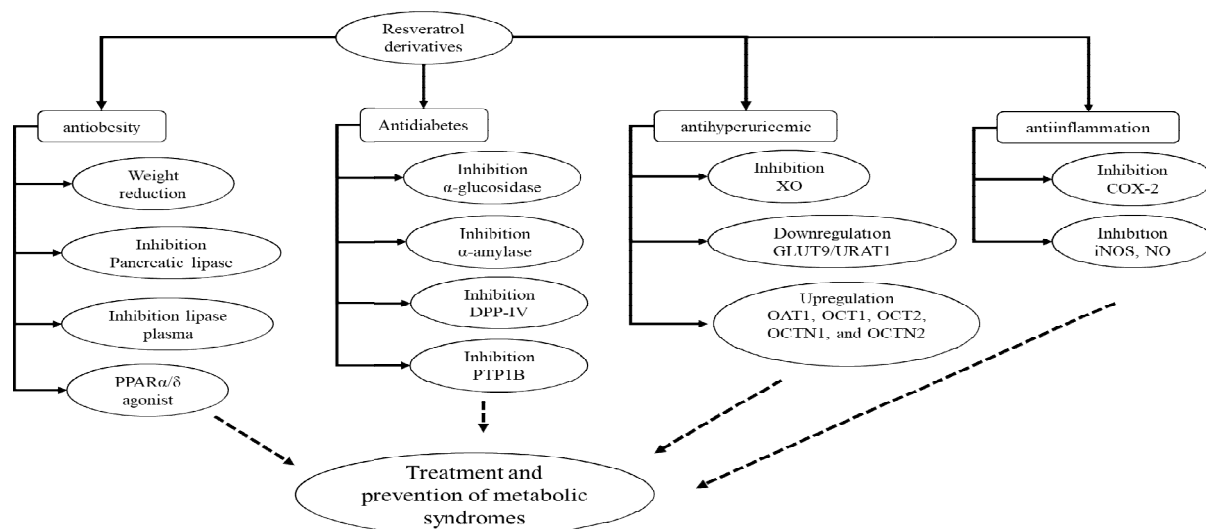


Fig.-3: Mechanism Action of Resveratrol Derivatives in the Prevention and Treatment of Metabolic Syndromes

### Vitisin A

Vitisin A (**10**) is a resveratrol tetramer isolated from ethanol extracts of *Vitis thunbergii* var. taiwaniana and *Ampelopsis brevipedunculata* var. hancei (Planch.) Rehder.<sup>48-49</sup> The pharmacological activities related with metabolic syndromes of vitisin A have been studied in animal model. Mice treated with vitisin A at 25 mg/kg bw showed a significant weight reduction as compared with obese mice.<sup>47</sup> Also, vitisin A also showed antidiabetes activity as presented by inhibition of  $\alpha$ -glucosidase as well as DPP-IV enzyme.<sup>48</sup> Interestingly, a study reported that vitisin A is a potent angiotensin converting enzyme inhibitor, showing its efficacy to reduce blood pressure.<sup>49</sup> These data show that vitisin A is an excellent candidate for the treatment and prevention of obesity, type 2 diabetes mellitus as well as hypertension. Hence, the natural product extract containing vitisin A may be used for alternative treatment and prevention of metabolic syndrome. However, due to the lack of clinical trial as well as safety assessment data, the development of this compound is still limited.

### Vaticanol C

Vaticanol C (**11**) is resveratrol tetramer that has been isolated from diverse Dipterocarpaceae species, including *Vatica rassak*, *Shorea roxburghii* and *Vatica pauciflora*.<sup>53-55</sup> This compound has been reported exhibiting various biological activities such as antioxidant, anticancer, anti-inflammatory as well as antiobesity.<sup>53,64</sup> In an experiment of antiobesity activity, vaticanol C was found activating PPAR- $\alpha$  and PPAR- $\beta/\delta$  both *in vitro* and *in vivo*. Therefore vaticanol C may efficiently reduce the body weight.<sup>56</sup> Hence, we suggest that plant containing vaticanol C is a promising therapeutic agent for treating metabolic syndromes in particular for patients with obesity. Unfortunately, the safety assessment as well as pharmacokinetic profile of this compound has not been evaluated.

Finally, we propose the mechanism of action of resveratrol derivatives in the prevention and treatment of metabolic syndrome (Fig.-3). It is presented that resveratrol derivatives tend to interfere with various targets and inhibit several enzymes which are directly associated with obesity, hyperuricemia, type 2 diabetes mellitus as well as inflammation, hence, possible to treat and prevent metabolic syndromes.

### CONCLUSION

Resveratrol derivatives present in nature have been investigated in pre and clinical trials. However, resveratrol derivatives are rarely studied due to their small amount quantity except mulberroside A and gnetin C. Some purified resveratrol derivatives from different kinds of plants exhibit greater pharmacological activity than that of its parental compound (trans-resveratrol). The relevant investigations have shown that resveratrol derivatives are a promising anti-diabetes, anti-cholesterol, anti-inflammatory, antihyperuricemic, as well as anti-obesity agent, thus possible to be applied in the prevention and treatment of metabolic syndromes. It should be noted that results from *in vitro* and *in vivo* studies are not always similar to those obtained from clinical studies due to the complex biological system. Accordingly, we suggest performing a large number of well-controlled and long-term clinical studies of resveratrol derivatives to warrant the pharmacological efficacy. There is also a need to observe whether the various pharmacological effect of resveratrol derivatives could give antagonist or synergistic effects. Although most of the scientific investigations on the pharmacological activities of resveratrol derivatives have shown its efficacy, however its exact mechanism of those compounds in the prevention and treatment of metabolic syndromes has not yet been fully studied and understood, hence further investigations are urgently needed. Finally, we also suggest that natural product extract contains high levels of resveratrol derivatives merit for being developed as an alternative medicine for the treatment and prevention of metabolic syndromes.

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