Review

Future molecular medicine from white frangipani (Plumeria alba L.): A review

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White frangipani (Plumeria alba L.) is tropical and subtropical plants, have been familiar used in many traditional medication as well as aromatherapy, especially for the flower part. Scientific study, but was not so many, reporting some pharmacological and toxicological effects of this plant which lead to more depth study at molecular level. This review describes the pharmacological and toxicological effect of the white frangipani and followed by its perspective on the future molecular medicine by identifying the protein target based on those biological effects. Hopefully this review could help scientist to get the summary from various study on white frangipani and raise the idea to study more about this plant at molecular level.

Key words: White frangipani, molecular medicine, traditional medication, plant.

INTRODUCTION

The family of Apocynaceae is widely distributed in tropic and subtropic regions, but it poorly plants up in the territory with a high temperature (El-kashef et al., 2015). The genera belongs to this family such as adenium, alstonia, alyxia, nerium, plumeria and vinca have been extensively reported having empirical evidence as folk medicines. However, due to the toxic milk latex of adenium, the plant was usually used for skin treatment such as to kill lice (Watt and Breyer-Brandwijk, 1933). Alstonia was traditionally used for respiratory disease (Shang et al., 2010), whereas alyxia was for post-natal care (Jamal et al., 2011). Nerium was empirically used for cancer treatment (Erdemoglu et al., 2003), and vinca was used in diabetic patient (Ghosh and Suryawanshi, 2001). Scientifically, those herbals have been reported having pharmacological effect such as antioxidant for adenium (Ebrahim et al., 2013), whereas alstonia is an herbal used for antivirus (Zhang et al., 2014). Alyxia is familiar to be used as antifungal (Rattanapan et al., 2012) while nerium and vinca are toxic herbals used for CNS depressant (Siddiqui et al., 1997) and antitumor (Cutts et al., 1960), respectively.

To be more focused, plumeria is one of interesting plants from Apocynaceae to be explored in term of its diversity as well as the medicinal usage. This plant could grow up to 7 m in height (Sloan et al., 2007), branching with a milky latex inside the elongated green leaves, barks and stems (Murugan and Inamdar, 1987). Plumeria is a flowering plant commonly called as frangipani with a perfume fragrant (Wiart, 2006). The color of the flower could be white, yellow, dark red, and its hybrids in five numbers of corollas. In certain indigenous people like in Bali Island of Indonesia, this flower is used to perform worships to their God (Sujarwo and Keim, 2017).

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Currently, the fragrant is having a high economic value to be used as an aromatherapy material (Verma, 2016).

The latex of frangipani have been extensively studied containing alkaloid and sterol compounds which pharmacologically active as antitumor (Graham et al., 2000), hypotensive and purgative (Gupta et al., 2016). The alkaloid such as plumerianine have been studied as anti-anaphylactic (Vijayalakshmi et al., 2011) whereas an abundance of sterol compounds such as lupeol, taraxerol and betulin also have reported as anti-inflammatory (Geetha and Varalakshmi, 2001), anticancer (Tan et al., 2011), and hypolipidemia (Tang et al., 2011). Among plumeria species, Plumeria rubra (red flower) has been the most studied species in scientific herbal medicinal plants. Instead, Plumeria alba (white frangipani) is also interesting to be explored due to its abundance resource as well as red frangipani.

Our previous study has found that the methanol extract of white frangipani leaves actively inhibit matrix metalloproteinase-9 (MMP9) with IC$_{50}$ 24.06 μg/ml (Anggoro, 2020). MMP9 is a zinc-dependent endopeptidase which involved in extracellular matrix (ECM) degradation. MMP9 was clinically indicated in a triple negative breast cancer, therefore has been potentially used as the protein target in cancer drug discovery (Putra et al., 2019). This finding prompts us to study more about the potential drug effect from this white frangipani.

In this review, we will elaborate the pharmacological effect of white frangipani as antimicrobe, antioxidant, antiparasite, agent for metabolic and degenerative diseases, and dermatology. The toxicological effect of this species will also be furtherly reviewed including in vitro and in vivo studies. In the perspective, we will discuss about the protein which could be targeted in those mentioned biological activities at molecular level. This review is hopefully able to ease researcher to discover a potential lead compound in drug discovery and development based on natural product resource, especially from white frangipani.

CHEMICAL CONSTITUENT OF WHITE FRANGIPANI

White frangipani contains chemical substances such as amyrin, scopoletin, iridoid isopluumericin, plumerein, plumeride cumarate and plumeride cumarate glycoside. The leaves and barks contain plumerin, resinic acid, fulvopluumericin, terpenoid mixture, sterol, and plumeride. Furthermore, the bark also contains cytotoxic iridoid, allamcin, allamandin, 2,5-dimethoxy-p-benzoquinone, plumercin and lirodindrin. The roots of white frangipani also contains iridoid, tannin and alkaloid (Shinde et al., 2014). The essential oil from the flower are composed of geraniol, citronellol, phenyl ethylalcohol and some linalool (Gupta et al., 2016).

The database of natural product compounds, http://bidd2.nus.edu.sg/NPASS/organism.php?org_id=NP O2827 list downs a number of chemical substance in white frangipani, that is, (+/-)-1,4-O-diferuloylsecosolarioscinol, betulin, lupeol, asam betunolat, (8Ar)-8A-hydroxy-3,3,6,6,8,8-hexamethyl-1,2-benzodioxine-5,7-dione, betulin, vitamin E, beta-amirin, friedelene, taraxerol, and 3-O-acetylbeutelin.

Figure 1 represents five natural compounds deposited in white frangipani. The sterol compounds of taraxerol, lupeol and betulin and also the coumarone in fulvopluumericin seem like having structure similar to the cholesterol esterase inhibitor. Moreover, the geraniol is rich of double bonds with OH terminal, suitable for antioxidant against 2-hydroxybiphenyl-3-monooxygenase. These are only a few structures in white frangipani that could be proposed for molecular medicine in the treatment of hyperlipidemia, cardiovascular etc. Figure 1 illustrate the structure of five chemical substances being identified in white frangipani.

PHARMACOLOGICAL ACTIVITY

Antimicrobial

The flower of white frangipani has been reported having antibacterial activities against Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus saprophyticus, Enterococcus faecalis and Serratia marcescens by using disc diffusion method (Syakira and Brenda, 2010). The methanolic-water (4:1) extract from this flower demonstrated the highest reading up to 13.33 mm inhibition zone towards E. coli at 80% concentration which is equivalent to the positive control, streptomycin. In the testing to S. saprophyticus, the 80% extract showed 10.33 mm of the zone which is lower than the positive control (19.67 mm). In P. vulgaris, the extract performed 12.33 mm of the zone which is also below the positive control (15 mm). The extract was then applied to S. marcescens demonstrating 11 mm of the zone which is lower than the control (17.33 mm). Although approximately the antibacterial activity of the extract is still below than the positive control, there are still potential activity of the extract as antibacterial agent, especially to E. coli. However, all extracts are still less potent than gentamycin as the second positive control. To all bacteria species, gentamycin showed above 20 mm of inhibition zone, whereas the 80% extract showed less than 15 mm of inhibition. White frangipani has been studied its biological activity against Propionibacterium acnes in the effort to formulate its leaves ethanolic extract into water leached-based ointment (Ningsih et al., 2017). The antiacne properties of white frangipani was indicated by 24 mm zone of inhibition on P. acne growth at 5 ppm of the extract in the ointment concentration. The alkaloid and saponin being contained in the leaves was believed...
to be responsible for the antiacne activity.

*Streptococcus pyogenes* is a bacteria to cause pharingitis and tonsillitis. Jiwantono et al. (2017) reported that the ethanolic extract of white frangipani flower disrupted the colony growth of this bacteria down to 7.81 mg/ml based on the minimum bactericidal concentration using dilution method (Jiwantono et al., 2017). Unfortunately, the minimum inhibition concentration could not be observed due to the inconsistency of the level of turbidance for each treated colony.

Instead of antibacterial effect from white frangipani has been well documented, its antifungal effect was also reported. The ethanolic extract of white frangipani flower was proposed to be a dental cleanser by evaluating it against *C. albicans* colony growth (Wadianur et al., 2018). The extract at the highest concentration 100% was observed to inhibit the fungus with the reduction of the concentration down to 3.080 × 10^8 CFU/ml from its starting concentration at 6.439 × 10^8 CFU/ml (negative control).

### Antioxidant

There have been well studied, that reactive oxygen stress (ROS) causing oxidized state associating with many pathologic condition such as cancer, inflammation, cardiovascular diseases etc. White frangipani has been reported to have antioxidant activity by extracting its flower using ethanol and acetic acid (Wrasiati et al., 2011). The ethanolic extract performed 18.19% antioxidant capacity against DPPH, whereas the acetic acid extract demonstrated 12.74% of its capacity as well. Although it is not that high capacity, the antioxidant activity of white frangipani flower could be contributed by its vitamin C substance as determined using 2,4-dinitrophenylhydrazine method. The vitamin C content in the flower is calculated as 3.08 and 3.13% for the ethanolic extract and acetic acid extract, respectively.

Dawood et al. (2016) reported the antioxidant activities of white frangipani leaves using various methods that is, FRAP, DPPH free radical scavenging and reducing power assay. The samples were prepared on methanolic extract and its crude polysaccharide. The antioxidant activities were observed for polysaccharide at a concentration 3 mg/ml showing a FRAP value of 0.0915 and 0.0901 μmol Fe (II)/g for methanolic extract and PAPs, respectively. Using DPPH method at the concentration of 3 mg/ml, the percentage inhibition was 94.28 and 84.18 for the methanolic extract and *Plumeria alba* polysaccharides (PAPs), respectively. However, the reducing power of the methanolic extract was higher than that of PAPs at a concentration 3 mg/ml.

### Antiparasite

White frangipani stem bark has been used in traditional medication in Ghana as antimalarial. An alternative way around to find antimalarial agent instead of Artemisinin
has been used for so long time, prompting the utilization of this plant to overcome malarial case. Scientific studies then reported that the aqueous extract (30-300 mg/kg) as well as dichloromethane/methanol (30-300 mg/kg) of this part of the plant showed significant effect towards mice infected by *Plasmodium berghei* (Boampong et al., 2013). Surprisingly, this is equivalent to the effect of artemether and lumefantrine, curatively, and sulfadoxine/pyrimethamine, prophylactically. However, the dichloromethane/methanol extract reduced the parasitemia curatively, (p≤ 0.05-0.01), but it was not prophylactically.

As mentioned before, that the fragrant smell of white frangipani has been used as aromatherapy. This fragrant comes from the content of essential oil having high value in beautification business. One study reported the utilization of this flower by distilling the essential oil using water distillation and it is applied for anti-repellant (Nurcahyo and Purgiyanti, 2017). The collected oil was then formulated in to gel bases with a concentration 5 to 10% demonstrating the preference of respondent to use formula 2 as the anti-repellant. This formula consists of menthol 7.5%, camphor 4%, olive virgin oil 20%, and essential oil of white frangipani 10%.

**Agent for metabolic and degenerative diseases**

Rheumatic arthritis is a chronic symptom of inflammatory diseases leading to cartilage destruction as well as its bone erosion. Although there have been drugs available for this symptoms such as NSAID and SAID, however, the adverse drug reaction such as gastrointestinal disorder making these drugs should be minimized in therapy. Study in 2014 reported the potency of white frangipani being used as antiarthritis (Choudhary et al., 2014). In this study, hydroalcoholic extracts (30:70) from white frangipani leaves was further fractionated into ethylacetate and n-buthanol extracts. These two extracts were administered orally to Sprague-Dawley arthritic rats induced by formaldehyde and Freund’s complete adjuvant. From the physical assessment and the histopathology test, the 100 and 200 mg/kg doses of ethylacetate extract and n-buthanol extract caused a significant (p≤0.05-0.01) reduction in paw swelling in both models. Erythrocyte sedimentation rate (ESR) and spleen weight decreased significantly (p < 0.01) in arthritic rats treated with extracts. Then, there was a significant improvement (p < 0.05) in thymus weight in ethylacetate extract treated rats whereas another significant improvement (p < 0.01) was also seen in hemoglobin level (Hb) in diclofenac treated group. Motor incoordination and nociceptive threshold were also significantly improved (p≤0.05-0.01).

Hyperlipidemia is one of the risk factors in cardiovascular diseases. The usage of synthetic hypolipidemic agent has been successfully lowering the lipid blood level. However, alongside with this, the toxicity of synthetic hypolipidemic agent such orlistat have been prompting the use of herbal medicine to overcome such metabolic disorder. Study by Rahman et al. (2014) reported the potential effect of white frangipani flower as hypolipidemic agent. Anti-cholesterol assay of the extracts was demonstrated by white frangipani extract with 52% of activity. This result shows the potency of white frangipani flower as the hypolipidemia although the activity is still not greater than simvastatin (92%) as the positive control. Diabetes is also metabolic disorder detected by hyperglycemia after post prandial status due to the insulin lack or resistance. This disease leads to many complications such cardiovascular and micro vascular disease. White frangipani was reported having hypoglycemic activities as evaluated by oral glucose tolerance test on mice (Kadébé et al., 2016).

**TOXICOLOGICAL ACTIVITY**

Along with the pharmacological activities of white frangipani have been well reported, the toxicological properties should be aware accordingly. It is well known that more potent compounds being drug, the more potential to be toxic. For example, digitalis leaves are used to treat heart failure, but it is toxic. The acute and sub-acute toxicities of white frangipani was conducted in Sprague-Dawley rats (Tessou et al., 2013). The hydroalcoholic extract of the roots was administered orally as a single dose of 5 g/kg for acute toxicity, whereas the dose was divided into three administrations that is, 250, 500 and 100 mg/kg for 28 days. Some parameters were then examined including the body weight and blood glucose which were continuously monitored every week. Other parameters such as hematological, biochemical, and a relative organ weight were also determined at the end of the 28 days administration. It was observed, that there was no acute toxicity in the mentioned dose. Further sub-acute toxicity test also demonstrated no dead was induced by the extract, up to 1000 mg/kg. In accordance, the tissue organ histologic parameter also did not show any changing during the white frangipani extract exposure, supporting that this extract did not have both acute and sub-acute toxicities.

In the cytotoxicity study, the flower of white frangipani has been evaluated against colorectal cancer cell model, that is, colo 205 as reviewed (Hanan et al., 2018). The sample was prepared in silver nanoparticle with a concentration 4.5 and 5.5 µg/ml exposed for 48 and 24 h, respectively. Both concentrations demonstrated cytotoxicity by apoptotic mechanism with the time/dose-dependent parameter (Mata et al., 2015). This result proposed that white frangipani flower was potential for anticancer especially for colorectal cancer. The white frangipani leaves extracted using dichloromethane.
(DCM) and tested its toxicity using brine shrimp lethality test (BSLT) (Hidajati and Qodriyah, 2018). BSLT is a simple method for cytotoxicity based on the killing ability of the test compounds on a simple zoological organism—brine shrimp (Artemia salina) (Harwig and Scott, 1971; Wu, 2014). The DCM extract was further extracted using hexane-ethylacetate showing LC₅₀ 54.448 µg/ml being suggested for further study for its potential as cancer cytotoxic agent.

**PERSPECTIVES ON BIOLOGICAL ACTIVITY AT MOLECULAR LEVEL**

In a decade, white frangipani has been studied for its potential effect as antimicrobial, antioxidant, antiparasite and agent for metabolic and degenerative diseases along with its toxicities either in vitro or in vivo experiment. Although those studies have been good for further development, however, the type of testing is limited for in vitro cellular as well as in vivo animal level. There is almost no study at molecular level for this plant.

It is well known that the study at molecular level is important to find the more selective pathway (Holmes, 1998). The less selective target is postulated as the more risk the drug to be toxic or having adverse side effect (Buckley and Sanders, 2000). Molecular level includes enzyme, receptor, signal transduction and nucleic acid as the drug target. Those drug targets interact with the drug through chemical interactions such as electrostatic, hydrogen and hydrophobic bondings. In this perspective, we will focus on enzyme and receptor, whereas for signal transduction and nucleic acid, it would be discussed in another review. For enzyme and receptor, the drug is commonly binding to the active site of the protein surrounded by important amino acid residues. The drug-protein binding stability is depending on their free energy of binding and drug’s structural conformation (Patrick, 2013).

To date, science and technology in protein (proteomic) has been greatly developed to facilitate studies on drug-protein binding at the molecular level (Lomenick et al., 2011). The gene of protein (enzyme and receptor) could be isolated from the cell of protein being deposited and then expressed into microorganism such as E. coli and observed as a protein recombinant (Gasser et al., 2008). This protein recombinant could be further studied either in silico or in vitro experiment. This part will tabulate the proteins being involved in the biological effect of white frangipani as reviewed above. These proteins have been crystallized and deposited in protein data bank (www.rcsb.org).

As presented in Table 1, the protein targets for antimicrobe are represented by aminopeptidase A, nicotinic acid mononucleotide adenyltransferase, beta-ketoacyl-acyl-carrier transferase and dihydroproteoate synthetase. Aminopeptidase A is an exopeptidase which hydrolyzes the N-terminal glutamic acid or aspartic acid. One of the inhibitors of this enzyme is amastatin, a natural peptide isolated from Streptomyces sp (Hiranuma et al., 1997). Nicotinic acid mononucleotide adenyllytransferase is an enzyme which indispensably catalyzing in the biosynthesis of NAD⁺ and NADP⁺. A study reported that this enzyme was inhibited by compound bearing – hydrazine and tricyclic scaffold (Sorci et al., 2009). Beta-ketoacyl-acyl-carrier transferase is the enzyme that involved in fatty acid biosynthesis system dissociation. This biosynthesis occurs in bacteria that could be inhibited by compounds with scaffold benzylidene-hydrazide (Lee et al., 2012). Dihydroproteoate synthetase is an enzyme in bacteria which catalyzes the reaction between (2-amino-4-hydroxy-7,8-dihydropyridine-6-yl)methyl diphosphate + 4-amino benzoate (PABA). The product, i.e. dihydrossoete and diphosphate were inhibited by sulfonamide drug. However, the dihydroproteoate synthetase has been resistant toward this sulfonamide (Wang et al., 1997).

In antioxidant, the protein targets are represented by glutathione reductase, human peroxidase (peroxidoxin) and 2-hydroxybiphenyl-3-monoxygenase. Glutathione reductase catalyzes the conversion of glutathione disulfide into glutathione which depends on the NADPH coenzyme. This reaction is important in maintaining the blood glucose level activated by flavin related compounds (Beutler, 1969). Human peroxidase or peroxidoxin regulates the intracellular concentration of H₂O₂ by reducing it into a more proper electron donating agent. This enzyme is activated by hydroquinone compound leading to the formation of DNA-adducts to the cell (György et al., 1993). 2-hydroxybiphenyl-3-monoxygenase is an oxoreductase catalyzing the reaction between 2-hydroxyphenyl and NADH to form the products that is, 2,3-hydroxybiphenyl and NAD⁺. The substrate of this enzyme is 2-hydroxybiphenyl, therefore, the inhibitor could be designed based on the similar structure with the substrate (Kanteev et al., 2015).

The protein targets of antiparasite are represented by lactate dehydrogenase, enoyl-acyl-carrier-protein reductase, actin II and pyridoxal-5-phosphate synthase. Lactate dehydrogenase (LDH) oxidizes lactic acid into pyruvic acid which is crucial for parasite life such as P. berghei. Gossypol, a natural compound from cotton seeds inhibits this enzyme with K₅₀ 1.4 µM towards LDH-B4 (Yu et al., 2001). Enoyl-acyl-carrier-protein reductase is an important enzyme to synthesize fatty acid in parasite through acetyl-malonyl-butyryl conversion. Pyridinone compounds have been reported having inhibition to this enzyme (Heath and Rock, 1995). Actin II is a protein which highly conserved in a various cell motility and expressed in all eukaryotic cells and contributes on parasite gliding motility. This protein could be inhibited by chondroamide, an analog by binding into the actin filament and blocking the growth of the parasite on the cell layer (Ma et al., 2013). Pyridoxal-5-phosphate...
Table 1. The protein, resourced cell, type of protein and PDB code could be targeting by white frangipani according to the biological activity at molecular level.

| Biological activity | Protein target | Resourced cells | Type of protein | PDB code |
|---------------------|----------------|-----------------|-----------------|----------|
| Antimicrobial       | Aminopeptidase A | *E. coli* | Enzyme | 1GYT (Strater et al., 1999) |
|                     | Nicotinic acid mononucleotide Adenylyltransferase | *S. aureus* | Enzyme | 2H29 (Han et al., 2006) |
|                     | Beta-ketoacyl-acyl-carrier transferase | *M. tuberculosis* | Enzyme | 1HZP (Scarsdale et al., 2001) |
|                     | Dihydropyrodocte synthetase | *Streptococcus pneumoniae* | Enzyme | 2VEF (Levy et al., 2008) |
| Antioxidant         | Glutathione reductase | *Homo sapiens* | Enzyme | 1K4Q (Savvides et al., 2002) |
|                     | Human peroxidase | *Homo sapiens* | Enzyme | 1PRX (Choi et al., 1998) |
|                     | Peroxidoxin | *Plasmodium falcifarum* | Enzyme | 4D73 (Staudacher et al., 2015) |
|                     | 2-hydroxybiphenyl-3-monoxygenase | *Pseudomonas nitroreducens* | Enzyme | 6EM0 (Bregman-Cohen et al., 2018) |
| Antiparasite        | Lactate dehydrogenase | *Plasmodium berghei* | Enzyme | 1OC4 (Winter et al., 2003) |
|                     | Enoyl-acyl-carrier-protein reductase | *Plasmodium berghei* | Enzyme | 3F4B (Yu et al., 2008) |
|                     | Actin II | *Plasmodium berghei* | Receptor | 4CBX (Vahokoski et al., 2014) |
|                     | Pyridoxal-5-phosphate synthase | *Plasmodium berghei* | Enzyme | 4ADS (Guédez et al., 2012) |
| Arthritis           | T cell receptor beta chains | *Homo sapiens* | Receptor | 2AXH (Li et al., 2005) |
|                     | PI3K gamma | *Homo sapiens* | Enzyme | 2A4Z (Camps et al., 2005) |
|                     | Immune receptor | *Homo sapiens* | Receptor | 4MCY (Scally et al., 2013) |
|                     | BTK mutant (F435T,K596R) | *Homo sapiens* | Enzyme | 3T9T (Kim et al., 2011) |
| Hyperlipidemia      | M37 lipase | *Photobacterium sp. M37* | Enzyme | 2ORY (Jung et al., 2008) |
|                     | Gastric lipase | *Homo sapiens* | Enzyme | 1HLG (Roussel et al., 1999) |
|                     | Cholesterol esterase | *Bos taurus* | Enzyme | 2BCE (Chen et al., 1998) |
|                     | Cholesterol oxidase | *Streptomyces sp. (strain SA-COO)* | Enzyme | 4U2S (Golden et al., 2014) |
| Diabetes            | Alpha-glucosidase | *Geobacillus sp. HTA-462* | Enzyme | 2ZE0 (Shirai et al., 2008) |
|                     | PPAR gamma | *Homo sapiens* | Receptor | 3ET0 (Artis et al., 2009) |
|                     | Murine 11b-hydroxysteroid dehydrogenase | *Mus musculus* | Enzyme | 1YS5 (Zhang et al., 2005) |
|                     | Glucokinase | *Homo sapiens* | Enzyme | 3IMX (Bebernitz et al., 2009) |

Synthase catalyzes the condensation of serine and homocysteine to form cystathionine. This enzyme is de novo synthesized by parasite as a crucial cofactor during erythrocytic schizogony. Compounds bearing pyridoxyl-tryptophan methyl esters have been reported to disrupt this enzyme biomolecular mechanism (Müller et al., 2009). Figure 2 illustrates the 3D structure of three proteins those are targeted for antimicrobial, antioxidant and antiparasite. Many proteins are involved in the molecular mechanism of rheumatoid arthritis but four of them are T cell receptor beta chains, PI3K gamma, immune receptor, BTK mutant (F435T, K596R). T cell receptor beta chains is commonly
found in the surface of T cell in lymphocyte. This protein has a function to recognize the peptide antigen bound to major histocompatibility complex. A MHC peptide has been studied as the T cell receptor beta chains antagonist, so that can reduce the antigen-receptor binding leading to arthritic healing activity (Lyons et al., 1996). PI3K gamma is encoded by PI3CG gene, so that the protein is belonged to pi3/pi4-kinase family, having a function to phosphorylate phosphoinositides on the 3-hydroxy group of the inositol ring. The phosphorylated product is important to modulate extracellular signal including inflammatory agent leading to rheumatoid arthritis. Compounds having structure thiazolidinones and 2-aminothecycles were two of reported agents to inhibit this such protein (Venable et al., 2010). Immune receptor is a membrane receptor having native ligand such as cytokine to proceed immunological response. Some antidepressants such as imipramine, clomipramine, and citalopram have been studied having antagonistic action against cytokine receptor (Vellucci, 2010). BTK mutant (F435T, K596R) is also a kinase playing a crucial role in oncogenic and proinflammatory signaling. This protein is blocked by imidazole compounds, as reported (Kim et al., 2011).

In hyperlipidemia, M37 lipase, gastric lipase, cholesterol esterase and cholesterol oxidase could be targeted as the protein which are responsible to this metabolic disorder. Lipase is an enzyme having a function to hydrolyze the triglyceride fatty acid forming triacylglycerol and free fatty acid. Fenfluramine and sibutramine are drugs for the treatment of obesity having lipolysis mechanism by inhibiting lipase enzyme (Heck et al., 2000). However, these two drugs have been withdrawn from the market in 1997 and 2010, respectively due to the serious adverse side effect on cardiovascular system (Kang and Park, 2012). Cholesterol esterase is an enzyme which catalyzes the hydrolysis of cholesterol ester to be free cholesterol and free fatty acid. The free cholesterol will be converted into many types like chylomicron, remnant, HDL, LDL and VLDL that could lead the hypercholesterolemia if the metabolisms were not well maintained. Compounds bearing p-nitrophenyl, isocoumarine and cholesteryl-N-alkyl carbamate have been reported to inhibit this enzyme (Hosie et al., 1987; Heynkanp et al., 2008). Cholesterol oxidase is another enzyme working on cholesterol metabolism by oxidizing the hydroxyl group of cholesterol into ketone. This enzyme is inhibited by some surfactants such as hydroxypolyethoxy dodecane, twen-20 and triton-X45 (Miner-Williams, 1980).

Four proteins including alpha-glucosidase, Peroxisome proliferated –activated receptor (PPAR) gamma, murine 11beta-hydroxysteroid dehydrogenase, and human glucokinase have been targeted in diabetic therapy. Alpha-glucosidase increases the blood glucose level by catalyzing the hydrolysis of a complex carbohydrate into glucose. This enzyme is inhibited by acarbose while the real mechanism of action is still remained unclear (Van de Laar et al., 2005). PPAR gamma receptor has a function as the regulator of lipid uptake and adipogenesis. A combined structure of coumarine and chalcone have been reported in activation of this receptor (agonist) to make the insulin receptor to be sensitized (Kim et al., 2019). Murine 11beta-hydroxysteroid dehydrogenase is a reductase having a microsomal short chain to catalyze glucocorticoid which is biologically active (cortisol) into inactive glucocorticoid (cortisone and 11-dehydrocortisone). In diabetes, an excess of cortisol could cause insulin intolerance and delay the wound healing, one of the complicated risk of diabetes mellitus. A small non-steroidal molecule called as BVT.2733 has been studied as the inhibitor of murine 11beta-hydroxysteroid dehydrogenase to low the hepatic PEPCK, glucose-6-phosphate mRNA, blood glucose and serum insulin concentration (Alberts et al., 2002). Human glucokinase converts glucose to glucose-6-phosphate through phosphorylation leads to glycollen synthesis. This enzyme is sensitive to oxidative stress of cells, especially to beta cells. Piraglavin, a small molecule bearing structure incorporating pyrimidine linked to chlorobenzene sulfone by amide chain with methyl cyclopentanone as the side chain being attached to the linker (Matschinsky and Porte Jr, 2010). Figure 3 illustrates the 3D structure of three proteins those are
targeted for rheumatoid arthritis, hyperlipidemia and diabetes.

CONCLUSION

This review has elaborated the molecular target that could be proposed for the molecular medicine of white frangipani (Plumeria alba L.). The availability of the crystal structure of the protein target facilitates the drug design from the identified chemical substance from this plant to be molecularly interacted with the binding site of the protein by in silico. This will lead the novel molecular medicine from white frangipani by speeding up the time of investigation. The future molecular medicine could be more efficient since the resource of this plant is quite abundant especially in tropical as well as subtropical areas.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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