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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 plumera 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 be also 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, scopotein, iridoid isoplumericin, plumerein, plumeride cumarate and plumeride cumarate glycoside. The leaves and barks contain plumierin, resinic acid, fulvoplumierin, terpeneoid mixture, sterol, and plumeride. Furthermore, the bark also contains cytotoxic iridoid, allamcin, allamandin, 2,5-dimethoxy-*p*-benzoquinone, plumericin and liriodindrin. 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=NPO2827 list downs a number of chemical substance in white frangipani, that is, (+/-)-1,4-O-diferuloyl-secoisolariciresionol, 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, friedeline, taraxerol, and 3-*O*-acetylbetulin.

Figure 1 represents five natural compounds deposited in white frangipani. The sterol compounds of taraxerol, lupeol and betuline and also the coumarone in fulvoplumericin 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

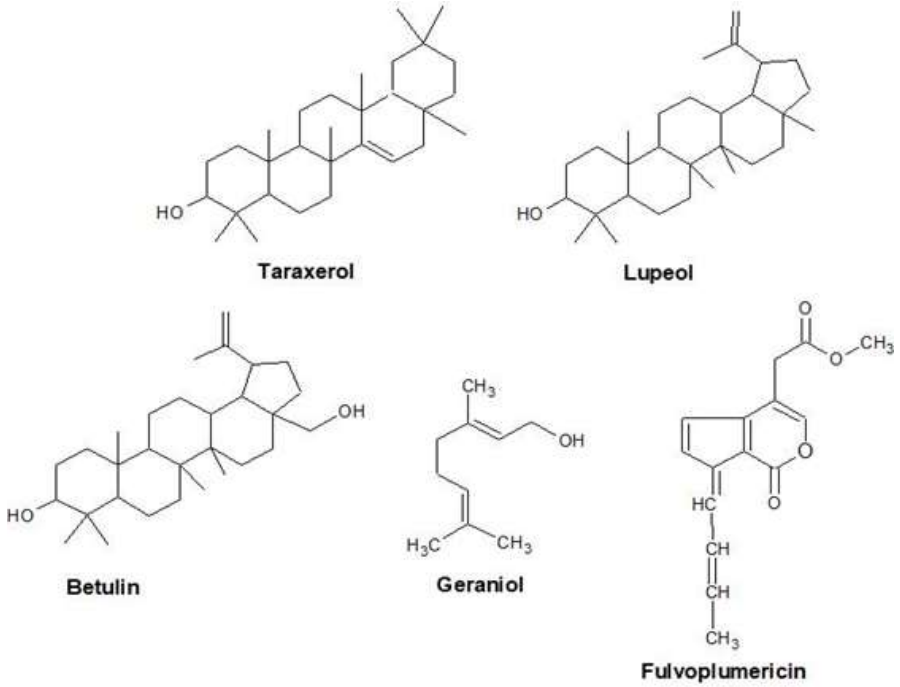

Figure 1. The structures of five chemical constituents identified in white frangipani. Source: Shinde et al. (2014) and Gupta et al. (2016).

to be responsible for the antiacne activity.

Streptococcus pyogene 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* polysacharrides (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, ($p \leq 0.05$-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 ($p \leq 0.05$-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 ($p \leq 0.05$-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 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 brime shirmp 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 LC_{50} 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 adenylyltransferase, beta-ketoacyl-acyl-carrier transferase and dihydropteroate 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 adenylyltransferase 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). Dihydropteroate synthetase is an enzyme in bacteria which catalyzes the reaction between (2-amino-4-hydroxy-7,8-dihydropteridin-6-yl)methyl diphosphate + 4-aminobenzoate (PABA). The product, i.e. dihydropteroate and diphosphate were inhibited by sulfonamide drug. However, the dihydropteroate 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-monooxygenase. 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 H_2O_2 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-monooxygenase is an oxidoreductase 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 K_i 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-butyril 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)
	Dihydropteorote 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	*Plasmidium falcifarum*	Enzyme	4D73 (Staudacher et al., 2015)
	2-hydroxybiphenyl-3-monooxygenase	*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	1Y5M (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

Figure 2. The 3D structure of aminopeptidase A (1GYT), glutathione reductase (1K4Q) and lactate dehydrogenase (1OC4) as visualized using Discovery Studio (www.accelrys.com) in surface models.

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-hydroxyl group of the inositol ring. The phosphorilated product is important to modulate extracellular signal including inflammatory agent leading to rheumatoid arthritis. Compounds having structure thiazolidinones and 2-aminoheterocycles 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 enzyme 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; Heynekamp 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 glycogen synthesis. This enzyme is sensitive to oxidative stress of cells, especially to beta cells. Piragliatin, 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

Figure 3. The 3D structure of T cell receptor beta chains (2AXH), M37 lipase (2ORY) and alpha-glucosidase (2ZE0) as visualized using Discovery Studio (www.accelrys.com) in surface models.

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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REFERENCES

Alberts P, Engblom L, Edling N, Forsgren M, Klingström G, Larsson C, Rönquist-Nii Y, Öhman B, Abrahmsén L (2002). Selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 decreases blood glucose concentrations in hyperglycaemic mice. Diabetologia 45(11):1528-1532.

Anggoro AB (2020). Uji Penghambatan Enzim Matrix Metalloproteinase-9 (MMP-9) Fraksi Aktif Daun Kamboja Putih *(Plumeria alba* L.*)*. Thesis. Sanata Dharma University, Yogyakarta.

Artis DR, Lin JJ, Zhang C, Wang W, Mehra U, Perreault M, Erbe D, Krupka HI, England BP, Arnold J, Plotnikov AN, Marimuthu A, Nguyen H, Will S, Signaevsky M, Kral J, Cantwell J, Settachatgull C, Yan DS, Fong D, Oh A, Shi S, Womack P, Powell B, Habets G, West BL, Zhang KYJ, Milburn MV, Vlasuk GP, Hirth KP, Nolop K, Bollag G, Ibrahim PN, Tobin JF (2009). Scaffold-based discovery of indeglitazar, a PPAR pan-active anti-diabetic agent. Proceedings of the National Academy of Sciences of the United States of America 106(1):262-267.

Bebernitz GR, Beaulieu V, Dale BA, Deacon R, Duttaroy A, Gao J, Grondine MS, Gupta RC, Kakmak M, Kavana M, Kirman LC, Liang J, Maniara WM, Munshi S, Nadkarni SS, Schuster HF, Stams T, St. Denny I, Taslimi PM, Vash B, Caplan S (2009). Investigation of Functionally Liver Selective Glucokinase Activators for the Treatment of Type 2 Diabetes. Journal of Medicinal Chemistry 52(19):6142-6152.

Beutler E (1969). Effect of flavin compounds on glutathione reductase activity: in vivo and in vitro studies. Journal of Clinical Investigation 48(10):1957-1966.

Boampong JN, Ameyaw EO, Kyei S, Aboagye B, Asare K, Afoakwah R, Boye A, Donfack JH (2013). In vivo antimalarial activity of stem bark extracts of *Plumeria alba* against *Plasmodium berghei* in imprinting control region mice. Reports in Parasitology 3:19.

Bregman-Cohen A, Deri B, Maimon S, Pazy Y, Fishman A (2018). Altering 2-Hydroxybiphenyl 3-Monooxygenase Regioselectivity by Protein Engineering for the Production of a New Antioxidant. ChemBioChem 19(6):583-590.

Buckley NA, Sanders P (2000). Cardiovascular Adverse Effects of Antipsychotic Drugs. Drug Safety 23(3):215-228.

Camps M, Rückle T, Ji H, Ardissone V, Rintelen F, Shaw J, Ferrandi C, Chabert C, Gillieron C, Françon B, Martin T, Gretener D, Perrin D, Leroy D, Vitte P, Hirsch E, Wymann MP, Cirillo R, Schwarz MK, Rommel C (2005). Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis. Nature Medicine 11(9):936-943.

Chen JCH, Miercke LJW, Krucinski J, Starr JR, Saenz G, Wang X, Spilburg CA, Lange LG, Ellsworth JL, Stroud RM. (1998). Structure of Bovine Pancreatic Cholesterol Esterase at 1.6 Å: Novel Structural Features Involved in Lipase Activation. Biochemistry 37(15):5107-5117.

Choi HJ, Kang SW, Yang CH, Rhee SG, Ryu SE (1998). Crystal structure of a novel human peroxidase enzyme at 2.0 Å resolution. Nature Structural Biology 5(5):400-406.

Choudhary M, Kumar V, Gupta P, Singh S (2014). Investigation of Antiarthritic Potential of *Plumeria alba* L. Leaves in Acute and Chronic Models of Arthritis. BioMed Research International 2014:1-12.

Cutts JH, Beer CT, Noble AL (1960). Biological Properties of Vincaleukoblastine , an Alkaloid in *Vinca rosea* Linn , with Reference to Its Antitumor Action. American Cancer Society 20(7):1023-1031.

Dawood HD, Hassan RA, Abdel-fattah SM (2016). Antioxidant Activity Evaluation of Methanolic Extract and Crude Polysaccharides from *Plumeria alba* L. Leaves. International Journal of Advance Research 4(5):1688-1701.

Ebrahim N, Kershi RM, Rastrelli L (2013). Free radical scavenging activity and anthocyanin in flower of *Adenium obesum* collected from Yemen. Journal of Pharmacy and Phytotherapeutics 1(5):5-7.

El-kashef DF, Hamed AN., Khalil HE, Kamel MS (2015). Triterpenes and sterols of family Apocynaceae (2013-1955), A review. Journal of Pharmacognosy and Phytochemistry 4(2):21-39.

Erdemoglu N, Küpeli E, Yeşilada E (2003). Anti-inflammatory and antinociceptive activity assessment of plants used as remedy in Turkish folk medicine. Journal of Ethnopharmacology 89(1):123-129.

Gasser B, Saloheimo M, Rinas U, Dragosits M, Rodríguez-Carmona E, Baumann K, Giuliani M, Parrilli E, Branduardi P, Lang C, Porro D, Ferrer P, Tutino M, Mattanovich D, Villaverde A (2008). Protein folding and conformational stress in microbial cells producing recombinant proteins: a host comparative overview. Microbial Cell Factories 7(1):1-18.

Geetha T, Varalakshmi P (2001). Anti-inflammatory activity of lupeol and lupeol linoleate in rats. Journal of Ethnopharmacology 76(1):77-80.

Ghosh S, Suryawanshi SA (2001). Effect of *Vinca rosea* extracts in treatment of alloxan diabetes in male albino rats. Indian Journal of Experimental Biology 39(8):748-759.

Golden E, Karton A, Vrielink A (2014). High-resolution structures of cholesterol oxidase in the reduced state provide insights into redox stabilization. Acta Crystallographica Section D Biological Crystallography 70(12):3155-3166.

Graham JG, Quinn ML, Fabricant DS, Farnsworth NR (2000). Plants used against cancer – an extension of the work of Jonathan Hartwell. Journal of Ethnopharmacology 73(3):347-377.

Guédez G, Hipp K, Windeisen V, Derrer B, Gengenbacher M, Böttcher B, Sinning I, Kappes B, Tews I (2012). Assembly of the Eukaryotic PLP-Synthase Complex from Plasmodium and Activation of the Pdx1 Enzyme. Structure 20(1):172-184.

Gupta M, Rakhi, Yadaf N, Saroj, Pinky, Siksha, Manisha, Priyanka, Amit, Rahul, Sumit, Ankit (2016). Research Article Phytochemical screening of leaves of *Plumeria alba* and *Plumeria acuminata*. Journal of Chemical and Pharmaceutical Research 8(5):354-358.

György L, Ross D, Bodell WJ (1993). Peroxidase activation of hydroquinone results in the formation of DNA adducts in HL-60 cells, mouse bone marrow macrophages and human bone marrow. Carcinogenesis 14(11):2329-2334.

Han S, Forman MD, Loulakis P, Rosner MH, Xie Z, Wang H, Danley DE, Yuan W, Schafer J, Xu Z (2006). Crystal Structure of Nicotinic Acid Mononucleotide Adenylyltransferase from *Staphyloccocus aureus*: Structural Basis for NaAD Interaction in Functional Dimer. Journal of Molecular Biology 360(4):814-825.

Hanan N, Chiu H, Ramachandran M, Tung W, Mohamad Zain N, Yahaya N, Lim V (2018). Cytotoxicity of Plant-Mediated Synthesis of Metallic Nanoparticles: A Systematic Review. International Journal of Molecular Sciences 19(6):1725.

Harwig J, Scott PM (1971). Brine Shrimp (*Artemia salina* L.) Larvae as a Screening System for Fungal Toxins. Applied Microbiology 21(6):1011-1016.

Heath RJ, Rock CO (1995). Enoyl-acyl carrier protein reductase (fabI) plays a determinant role in completing cycles of fatty acid elongation in *Escherichia coli*. Journal of Biological Chemistry 270(44):26538-26542.

Heck AM, Yanovski JA, Calis KA (2000). Orlistat, a new lipase inhibitor for the management of obesity. Pharmacotherapy 20(3):270-279.

Heynekamp JJ, Hunsaker LA, Vander Jagt TA, Royer RE, Deck LM, Vander Jagt DL (2008). Isocoumarin-based inhibitors of pancreatic cholesterol esterase. Bioorganic and Medicinal Chemistry 16(9):5285-5294.

Hidajati N, Qodriyah (2018). from White Frangipani Leaves (*Plumeria alba*). In Proceedings of the Seminar Nasional Kimia - National Seminar on Chemistry (SNK 2018) Toxicity, Surabaya: Atlantis Press.

Hiranuma T, Iwao K, Kitamura K, Matsumiya T, Oka T (1997). Almost complete protection from [Met5]-enkephalin-Arg6-Gly7-Leu8 (Met-enk-RGL) hydrolysis in membrane preparations by the combination of amastatin, captopril and phosphoramidon. Journal of Pharmacology and Experimental Therapeutics 281(2):769-774.

Holmes EC (1998). Molecular epidemiology and evolution of emerging infectious diseases. British Medical Bulletin 54(3):533-543.

Hosie L, Sutton LD, Quinn DM (1987). p-Nitrophenyl and cholesteryl-N-alkyl carbamates as inhibitors of cholesterol esterase. Journal of Biological Chemistry 262(1):260-264.

Jamal JA, Ghafar ZA, Husain K (2011). Medicinal Plants used for Postnatal Care in Malay Traditional Medicine in the Peninsular Malaysia. Pharmacognosy Journal 3(24):15-24.

Jiwantono F, Purwanta M, Setiawati Y (2017). Uji Efektifitas Ekstrak Bunga Kamboja (*Plumeria alba*) Sebagai Antibakteri Terhadap Streptococcus pyogenes. Jurnal Kedokteran Syiah Kuala 17(3):147-155.

Jung S, Jeong DG, Lee MS, Lee J, Kim HK, Ryu SE, Park BC, Kim JH, Kim SJ (2008). Structural basis for the cold adaptation of psychrophilic M37 lipase from *Photobacterium lipolyticum*. Proteins: Structure, Function, and Bioinformatics 71(1):476-484.

Kadébé ZT, Metowogo K, Bakoma B, Poevi Lawson-Evi S, Eklu-Gadegbeku K, Aklikokou K, Gbeassor M (2016). Antidiabetic Activity of *Plumeria Alba* Linn (Apocynaceae) Root Extract and Fractions in Streptozotocin-Induced Diabetic Rats. Tropical Journal of Pharmaceutical Research 15(1):87.

Kang JG, Park C (2012). Anti-Obesity Drugs: A Review about Their Effects and Safety. Diabetes and Metabolism Journal 36(1):13.

Kanteev M, Bregman-Cohen A, Deri B, Shahar A, Adir N, Fishman A (2015). A crystal structure of 2-hydroxybiphenyl 3-monooxygenase with bound substrate provides insights into the enzymatic mechanism. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics 1854(12):1906-1913.

Kim K, Maderna A, Schnute ME, Hegen M, Mohan S, Miyashiro J, Lin L, Li E, Keegan S, Lussier J, Wrocklage C, Nickerson-Nutter CL, Wittwer AJ, Soutter H, Caspers N, Han S, Kurumbail R, Dunussi-Joannopoulos K, Douhan J, Wissner A (2011). Imidazo[1,5-a]quinoxalines as irreversible BTK inhibitors for the treatment of rheumatoid arthritis. Bioorganic and Medicinal Chemistry Letters 21(21):6258-6263.

Kim SH, Hong SH, Park YJ, Sung J, Suh W, Lee KW, Jung K, Lim C, Kim JH, Kim H, Park KS, Park SG (2019). MD001, a Novel Peroxisome Proliferator-activated Receptor α/γ Agonist, Improves Glucose and Lipid Metabolism. Scientific Report 9(1656):1-12.

Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van Weel C (2005). Alpha-glucosidase inhibitors for type 2 diabetes mellitus C. M. and E. D. Group (ed). Netherland: John Wiley & Sons, Ltd. http://dx.doi.org/10.1002/14651858.CD003639.pub2

Lee JY, Jeong K, Shin S, Lee J, Kim Y (2012). Discovery of novel selective inhibitors of *Staphylococcus aureus* β-ketoacyl acyl carrier protein synthase III. European Journal of Medicinal Chemistry 47(1):261-269.

Levy C, Minnis D, Derrick JP (2008). Dihydropteroate synthase from *Streptococcus pneumoniae*: structure, ligand recognition and mechanism of sulfonamide resistance. Biochemical Journal 412(2):379-388.

Li H, Van Vranken S, Zhao Y, Li Z, Guo Y, Eisele L, Li Y (2005). Crystal structures of T cell receptor β chains related to rheumatoid arthritis. Protein Science 14(12):3025-3038.

Lomenick B, Olsen RW, Huang J (2011). Identification of Direct Protein Targets of Small Molecules. ACS Chemical Biology 6(1):34-46.

Lyons DS, Lieberman SA, Hampl J, Boniface JJ, Chien Y, Berg LJ, Davis MM (1996). A TCR binds to antagonist ligands with lower affinities and faster dissociation rates than to agonists. Immunity 5(1):53-61.

Ma CI, Diraviyam K, Maier ME, Sept D, Sibley LD (2013). Synthetic Chondramide A Analogues Stabilize Filamentous Actin and Block Invasion by *Toxoplasma gondii*. Journal of Natural Products 76(9):1565-1572.

Mata R, Reddy Nakkala J, Rani Sadras S (2015). Catalytic and biological activities of green silver nanoparticles synthesized from *Plumeria alba* (frangipani) flower extract. Materials Science and Engineering C 51:216-225.

Matschinsky F, Porte Jr D (2010). Glucokinase activators (GKAs) promise a new pharmacotherapy for diabetics. F1000 Medicine Reports 5(June):1-5.
Miner-Williams W (1980). Surfactant inhibition of cholesterol oxidase. Clinica Chimica Acta 101(1):77-84.
Müller IB, Wu F, Bergmann B, Knöckel J, Walter RD, Gehring H, Wrenger C (2009). Poisoning Pyridoxal 5-Phosphate-Dependent Enzymes: A New Strategy to Target the Malaria Parasite Plasmodium falciparum A. Lewin (ed). PLoS ONE 4(2):e4406.
Murugan V, Inamdar JA (1987). Organographic distribution, structure and ontogeny of lactifers in *Plumeria alba* Linn. Plant Science 97(1):25-31.
Ningsih DR, Zusfahair, Kartika D, Lestari IT (2017). Synthesis of Anti-Acne Ointment of Ethanol Extract of White Plumeria Leaves (*Plumeria Alba* L.). In IOP Conference Series: Materials Science and Engineering 172:1-9.
Nurcahyo H, Purgiyanti (2017). Pemanfaatan Bunga Kamboja (*Plumeria alba*) Sebagai Aromaterapi. Jurnal Para Pemikir 6(1):121-123.
Patrick LG (2013). An Introduction to Medicinal Chemistry fifth. Intergovernmental Panel on Climate Change (ed). Cambridge: Cambridge University Press pp. 10-13.
Putra KC, Nugroho ES, Wisnumurti YK, Dewa SP, Jati BWP, Tiara R, Setyaningsih D, Hariono M (2019). In silico Study of Thioguanine Derivatives As Hemopexin Matrix Uji Aktivitas Turunan Thioguanine Terhadap Hemopexin Matrix Metalloproteinase9 (PEX-9) In silico 1(2):17-24.
Rahman H, Reddy VB, Ghosh S, Mistry SK, Pant G, Sibi G (2014). Antioxidant, Cytotoxic and Hypolipidemic Activities of *Plumeria alba* L. and *Plumeria rubra* L. American Journal of Life Sciences 2(6):11-15.
Rattanapan J, Sichaem J, Tip-pyang S. (2012). Chemical constituents and antioxidant activity from the stems of *Alyxia reinwardtii*. Records of Natural Products 6(3):288-291.
Roussel A, Canaan S, Egloff M, Rivière M, Dupuis L, Verger R, Cambillau C (1999). Crystal Structure of Human Gastric Lipase and Model of Lysosomal Acid Lipase, Two Lipolytic Enzymes of Medical Interest. Journal of Biological Chemistry 274(24):16995-17002.
Savvides SN, Scheiwein M, Böhme CC, Arteel GE, Karplus PA, Becker K, Schirmer RH (2002). Crystal Structure of the Antioxidant Enzyme Glutathione Reductase Inactivated by Peroxynitrite. Journal of Biological Chemistry 277(4):2779-2784.
Scally SW, Petersen J, Law SC, Dudek NL, Nel HJ, Loh KL, Wijeyewickrema LC, Eckle SBG, Van Heemst J, Pike RN, McCluskey J, Toes RE, La Gruta NL, Purcell AW, Reid HH, Thomas R, Rossjohn J (2013). A molecular basis for the association of the HLA-DRB1 locus, citrullination, and rheumatoid arthritis. The Journal of Experimental Medicine 210(12):2569-2582.
Scarsdale JN, Kazanina G, He X, Reynolds KA, Wright HT (2001). Crystal Structure of the Mycobacterium tuberculosis β-Ketoacyl-Acyl Carrier Protein Synthase III. Journal of Biological Chemistry 276(23):20516-20522.
Shang J, Cai X, Zhao Y, Feng T, Luo X (2010). Pharmacological evaluation of *Alstonia scholaris*: Anti-tussive, anti-asthmatic and expectorant activities. Journal of Ethnopharmacology 129(3):293-298.
Shinde PR, Patil PS, Bairagi VA (2014). Phytopharmacological Review of Plumeria species. Scholars Academic Journal of Pharmacy 3(2):217-227.
Shirai T, Hung VS, Morinaka K, Kobayashi T, Ito S (2008). Crystal structure of GH13 α-glucosidase GSJ from one of the deepest sea bacteria. Proteins: Structure, Function, and Bioinformatics 73(1):126-133.
Siddiqui BS, Sultana R, Begum S, Zia A, Suria A (1997). Cardenolides from the Methanolic Extract of *Nerium oleander* Leaves Possessing Central Nervous System Depressant Activity in Mice. Journal of Natural Products 60(6):540-544.
Sloan SA, Zimmerman JK, Sabat AM (2007). Phenology of *Plumeria alba* and its Herbivores in a Tropical Dry Forest. Biotropica 39(2):195-201.
Sorci L, Pan Y, Eyobo Y, Rodionova I, Huang N, Kurnasov O, Zhong S, MacKerell AD, Zhang H, Osterman AL (2009). Targeting NAD Biosynthesis in Bacterial Pathogens: Structure-Based Development of Inhibitors of Nicotinate Mononucleotide Adenylyltransferase NadD. Chemistry and Biology 16(8):849-861.
Staudacher V, Djuika CF, Koduka J, Schlossarek S, Kopp J, Büchler M, Lanzer M, Deponte M (2015). *Plasmodium falciparum* antioxidant protein reveals a novel mechanism for balancing turnover and inactivation of peroxiredoxins. Free Radical Biology and Medicine 85:228-236.
Strater N, Sherratt DJ, Colloms SD (1999). X-ray structure of aminopeptidase A from *Escherichia coli* and a model for the nucleoprotein complex in Xer site-specific recombination. The EMBO Journal 18(16):4513-4522.
Sujarwo W, Keim AP (2017). Ethnobotanical Study of Traditional Building Materials from the Island of Bali, Indonesia. Economic Botany 71(3):224-240.
Syakira MH, Brenda L (2010). Antibacterial Capacity of *Plumeria alba* Petals. International Journal of Pharmacological and Pharmaceutical Sciences 4(8):1203-1205.
Tan B, Shi H, Ji G, Xie J (2011). Effects of taraxerol and taraxerol acetate on cell cycle and apoptosis of human gastric epithelial cell line AGS. Journal of Chinese integrative medicine 9(6):638-42.
Tang J, Li JG, Qi W, Qiu W, Li PS, Li B, Song B (2011). Inhibition of SREBP by a Small Molecule, Betulin, Improves Hyperlipidemia and Insulin Resistance and Reduces Atherosclerotic Plaques. Cell Metabolism. 13(1):44-56.
Tessou KZ, Lawson-Evi P, Metowogo K, Diallo A, Eklu-Gadegkeku K, Aklikokou K, Gbeassor M (2013). Acute and Sub-Acute Toxicity Studies of *Plumeria alba* Linn. (Apocynaceae) Hydroalcoholic Extract in Rat. International Journal of Biomedical Science 9(4):255-259.
Vahokoski J, Bhargav SP, Desfosses A, Andreadaki M, Kumpula EP, Martinez SM, Ignatev A, Lepper S, Frischknecht F, Sidén-Kiamos I, Sachse C, Kursula I (2014). Structural Differences Explain Diverse Functions of *Plasmodium Actins*. PLoS Pathogens 10(4):e1004091.
Vellucci S V (2010). Cytokines, Behavior, and Affective Disorders. New Insights to Neuroimmune Biology. 1. ed. Cambridge: Elsevier Inc. 12:237-254
Venable J, Ameriks M, Blevitt J, Thurmond R, Fung-Leung WP (2010). Phosphoinositide 3-Kinase Gamma (PI3Kγ) Inhibitors for the Treatment of Inflammation and Autoimmune Disease. Recent Patents on Inflammation and Allergy Drug Discovery 4(1):1-15.
Verma S (2016). Multipurpose Ornamental Plant *Plumeria rubra* Linn (Apocynaceae). International Jounal of Scientific Research in Science and Tecnology 2(4):646-649.
Vijayalakshmi A, Ravichandiran V, Velraj M, Hemalatha S, Sudharani G, Jayakumari S (2011). Anti–anaphylactic and anti–inflammatory activities of a bioactive alkaloid from the root bark of *Plumeria acutifolia* Poir. Asian Pacific Journal of Tropical Biomedicine 1(5):401-405.
Wadianur F, Hidayati L, Rahayu YC (2018). Effectiveness Of Cambodia White Flower Extract (*Plumeria alba* L.) As Denture Cleanser On The Growth Of *Candida albicans* In Base Material Of Artificial Teeth Nylon Thermoplastic (Valplast). Pustaka Kesehatan 6(1):161.
Wang P, Read M, Sims PFG, Hyde JE (1997). Sulfadoxine resistance in the human malaria parasite *Plasmodium falciparum* is determined by mutations in dihydropteroate synthetase and an additional factor associated with folate utilization. Molecular Microbiology 23(5):979-986.
Watt JM, Breyer-Brandwijk MG (1933). The Medicinal and Poisonous Plants of Southern Africa: Being an Account of their Medicinal Uses, Chemical Composition, Pharmacological Effects and Toxicology in Man and Animal. Nature 132(3331):336-336.
Wiart C (2006). Medicinal Plants of Asia and the Pacific. London: CRC Press Taylor & Francis Group. 250 p.
Winter VJ, Cameron A, Tranter R, Sessions RB, Brady RL (2003). Crystal structure of *Plasmodium berghei* lactate dehydrogenase indicates the unique structural differences of these enzymes are shared across the Plasmodium genus. Molecular and Biochemical Parasitology 131(1):1-10.
Wrasiati LP, Wirawan IGP, Bagiada NA, Astawa INM (2011). Antioxidant capacity of frangipani (*Plumeria alba*) Powder Extract. Indonesian Journal of Biomedical Sciences 5(2):1-11.
Wu C (2014). An important player in brine shrimp lethality bioassay : The solvent. Journal of Advance Pharmaceutical tecnology and

Research 5(1):57-58.
Yu M, Kumar TRS, Nkrumah LJ, Coppi A, Retzlaff S, Li CD, Kelly BJ, Moura PA, Lakshmanan V, Freundlich JS, Valderramos J, Vilcheze C, Siedner M, Tsai JHC, Falkard B, Sidhu A bir S, Purcell LA, Gratraud P, Kremer L, Waters AP, Schiehser G, Jacobus DP, Janse CJ, Ager A, Jacobs WR, Sacchettini JC, Heussler V, Sinnis P, Fidock DA (2008). The Fatty Acid Biosynthesis Enzyme FabI Plays a Key Role in the Development of Liver-Stage Malarial Parasites. Cell Host and Microbe 4(6):567-578.
Yu Y, Deck JA, Hunsaker LA, Deck LM, Royer RE, Goldberg E, Vander Jagt DL (2001). Selective active site inhibitors of human lactate dehydrogenases A4, B4, and C4. Biochemical Pharmacology 62(1):81-89.
Zhang J, Osslund TD, Plant MH, Clogston CL, Nybo RE, Xiong F, Delaney JM, Jordan SR (2005). Crystal Structure of Murine 11β-Hydroxysteroid Dehydrogenase 1: An Important Therapeutic Target for Diabetes. Biochemistry 44(18):6948-6957.
Zhang L, Zhang CJ, Zhang D, Wen J, Zhao X, Li Y, Gao K (2014). An unusual indole alkaloid with anti-adenovirus and anti-HSV activities from *Alstonia scholaris*. Tetrahedron Letters 55(10):1815-1817.