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Review Article

A Mini Review on Phytochemical Constituents and Pharmacological Activities of *Adenium obesum*

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ABSTRACT

Adenium obesum is a common plant found in many households in Malaysia. Its phytochemical constituents are believed to have contributed to its vast medicinal properties. Five types of compounds were isolated and identified from the plant, namely cardiac glycosides, pregnanes, triterpenes, flavonoids and carbohydrates. These compounds confer the plant its reported pharmacological activities such as antibacterial, antiviral, anticancer, antioxidant, immunomodulation and antiparasitic effects. The plant's antibacterial effects against some bacterial strains such as *Proteus mirabilis* and *Pseudomonas aeruginosa* were investigated while its antiviral activity was tested against H1N1. Its anticancer activity was found to be mediated through the hedgehog/GLI signalling pathway. For the immunomodulatory effect, *A. obesum* was found to promote proliferation of B and T cells. This review outlines in detail the pharmacological activities of *A. obesum* while further correlating these activities with the phytochemical constituents present.

Keywords: Adenium obesum, natural product, pharmacological activity, phytochemicals

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INTRODUCTION

Adenium obesum (A. obesum) or more commonly known as the desert rose or Sabi star, is native to the Sahal region, south of Sahara Africa in Oman (Al-Aklabi et al., 2016). This particular bonsai plant is mainly used as an ornamental plant typically in Malaysian houses as it grows very well in tropical climates (Al-

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Aklabi et al., 2016; Al-Ghudani & Hossain, 2015; Pullaih, 2006). Characteristics of the plant include its height averaging at three to four meters, thick trunk, smooth green bark, stems and leaves exuding a milky sap and funnel-shaped flowers with five red lobes (Figure 1). *A. obesum* belongs to the Apocynaceae family and is commonly considered a medicinal plant (Al-Ghudani & Hossain, 2015; Hossain et al., 2014a; Santapau & Henry, 1973).

Figure 1. The Distinct Morphological Characteristics of the *A. obesum* Flower

Conventionally, almost every part of *A. obesum* has been used in various therapeutic strategies. This may be due to the presence of active compounds in almost every part of the plant. Venereal diseases has been treated using extract obtained from the plant in Oman while the root and bark are made into lotion for the elimination of lice (Al-Ghudani & Hossain, 2015; Hossain et al., 2017; Tijjani et al., 2012). For the treatment of bacterial infections, the latex of the plant has been used, while Nigerians utilise the entire plant for its anti-parasitic properties. There are reports which suggest the use of this plant as an arbotifacient. It has also been recently suggested that *A. obesum* has the ability to cure bone dislocations, rheumatism, sprains and paralysis. In addition, topical application of the plant may potentially cure skin infections (Al-Ghudani and Hossain, 2015; Hossain et al., 2017; Versiani, et al., 2014).

In this review, the phytochemicals in the plant and their respective pharmacological actions will be further

elaborated. This review will also provide insights into the ways the pharmacological actions are initiated and possible future directions that may lead to increased awareness of the therapeutic potential of this plant.

PHYTOCHEMICAL CONSTITUENTS OF *A. OBESUM*

Approximately, 50 chemical compounds have been identified and isolated through various extraction and identification methods in previous studies. The five classes of the 50 compounds are cardiac glycosides, pregnanes, triterpenes, flavonoids and carbohydrates.

Cardiac Glycosides

These compounds are C_{23} cardenolides which share a common steroid structure, whereby a sugar portion is attached to one or more non-sugar molecules. The sugar portion gives the compound its solubility which is essential for its absorption and distribution in the body (Pengelly, 2004). These compounds also possess lactone rings that attach to the β position at carbon 17 (Pengelly, 2004; Ramawat & Merillon, 2010). Presently, 40 such compounds are discovered in the plant, making it the major chemical constituent of the plant (Versiani et al., 2014). These include aglycones and obebioside B (oleandri-genin β-d-glucopyranosyl-(1-4)-β-d-thevetoside), the main cardiac glycoside of the plant (Yamauchi & Abe, 1990a; Yamauchi & Abe, 1990b; Versiani et al., 2014). The solvents used for the extraction of these compounds are chloroform, ethyl acetate, benzene and butanol. All parts of the plant can be used, including the flowers, roots, bark and leaves (Akbar & Al-Yahya, 2011; Versiani et al., 2014).

Through various studies conducted, cardiac glycosides were found to exhibit positive inotrophic effect, increased atrial and ventricular myocardial excitability and decreased rate of atrioventricular conduction (Ahmad & Basha, 2007; Erdmann, 1981; Glynn, 1957; Hoffmann & Cole, 1976; Newman et al., 2008; Versiani et al., 2014).

Pregnanes

About four compounds from this class are currently known to be present in the *A. obesum* plant. They are 12β-hydroxy-pregna-4,6,16-triene-3,20-dione, 12β-hydroxypregna-4,16-diene-3,20-dione, 12β-hydroxypregna-4,6-diene-3,20-dione and 12β-hydroxypregna-4-ene-3,20-dione (Figure 2), which all share the four or six or 16-ene-20-one system (Bai et al, 2007; Nakamura et al., 2000; Pengelly, 2004; Yamauchi & Abe, 1990a). They are the C_{23} steroids and it is speculated that the unsaturation at the C_{17} gives the compounds a cytotoxic capacity.

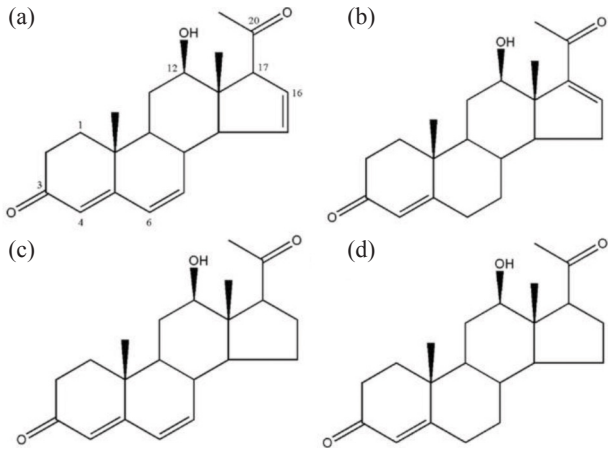

Figure 2. Chemical structures of: (a) 12β-hydroxy-pregna-4,6,16-triene-3,20-dione, (b) 12β-hydroxypregna-4,16-diene-3,20-dione, (c) 12β-hydroxypregna-4,6-diene-3,20-dione, and (d) 12β-hydroxypregna-4-ene-3,20-dione

Triterpenes

In *A. obesum,* two triterpenes have been isolated thus far, the lup-20(29)-ene-3, 28-diol (more commonly known as betulin) and dihydroifflaionic acid (Figure 3) (Tijjani et al., 2012; Versiani et al, 2014). These two compounds consist of a C_{27} skeleton derived from a C_{30} precursor which is squalene (Pengelly, 2004; Ramawat & Merillon, 2010).

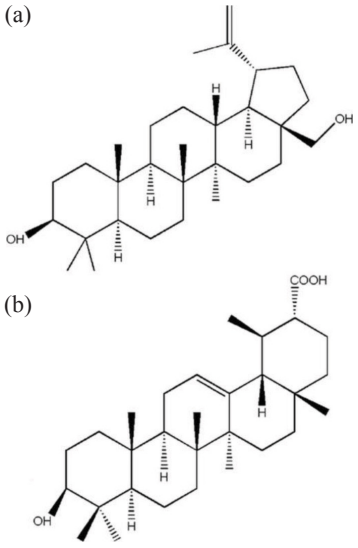

Figure 3. Chemical structures of (a) betulin and (b) dihydroifflaionic acid

Flavonoids

The two subclasses of flavonoids, the flavonols and anthocyanins, were isolated from *A. obesum* (Versiani et al., 2014). The flavonols are quercetin 3,3'-dimethylether and kaempferol 3-methyl ether, and the anthocyanin is cyanindin 3-O-(4-O-α-L-rhamnopyranosyl)-β-D-galactopyranoside (Figure 4) (Alseini, 2014; Versiani et al., 2014; Hossain et al., 2017). These compounds appear as yellow and white plant pigments. Antioxidant activity of the plant is believed to be associated with the presence of these compounds (Alseini, 2014; Al-Ghudani & Hossain, 2015). The redox property of the compounds allows them to act as reducing agents in the antioxidant system (Alseini, 2014; Pengelly, 2004). Other than that, these compounds may also play a role against diabetes mellitus and hyperlipidaemia (Alseini, 2014). Hossain et al. (2017) found that ethyl acetate extract of *A. obesum* stem contains flavonoids 5,7,3′,4′-tetrahydroxy flavone and 3,5,7,3′,4′,5′-hexahydroxy flavone (Figure 5). In addition, Meda et al. (2016) discovered four flavonols in the plant, including two quercetin glycosides (rutin and isoquercitrin) and two kaempferol glycosides (kaempferol 3-O-rutinoside and kaempferol 3-O-glucoside).

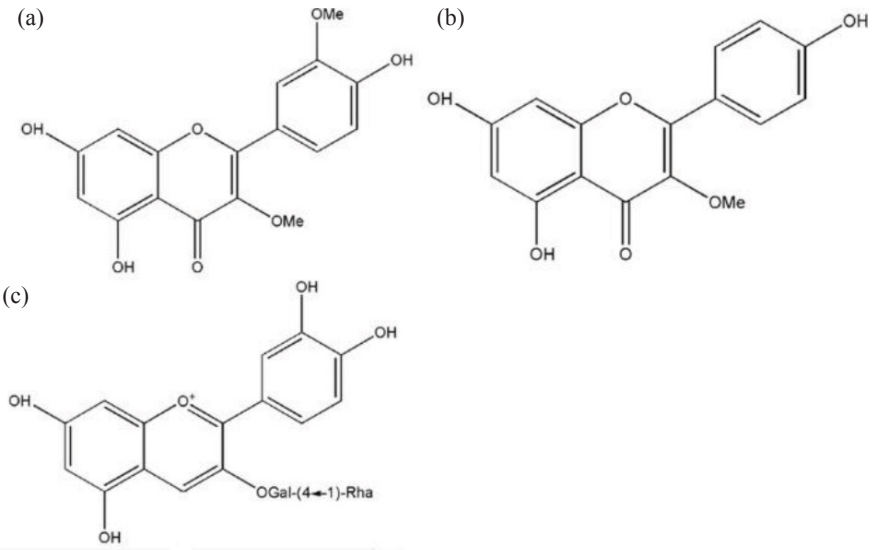

Figure 4. Chemical structures of: (a) quercetin 3,3'-dimethylether, (b) kaempferol 3-methyl ether and (c) cyanindin 3-O-(4-O-α-L-rhamnopyranosyl)-β-D-galactopyranoside

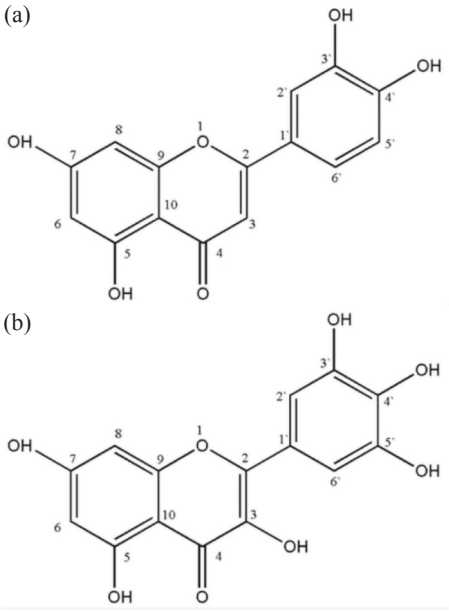

Figure 5. Chemical structures of (a) 5,7,3',4'-tetrahydroxy flavone and (b) 3,5,7,3',4',5'-hexahydroxyflavone

Carbohydrates

A carbohydrate compound was obtained through methanol extraction of *A. obesum*. The compound, which is known as 4-O-β-D-glucopyranosyl-D-cymaritol (Figure 6) was confirmed by structural comparison with an authentic sample which was obtained from reduction of strophanthobiose (Ramawat & Merillon, 2010; Versiani et al., 2014).

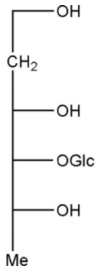

Figure 6. Chemical structure of 4-O-β-D-glucopyranosyl-D-cymaritol

PHARMACOLOGICAL ACTIVITIES OF *A. OBESUM*

As *A. obesum* possesses a considerable amount of bioactive compounds, it exhibits vast pharmacological activities and have a widespread usage in the traditional medication (Al-Aklabi et al., 2016). The plant is particularly renowned as a form

of medication in the West African region because essential drugs are usually not available due to high cost or a lack of coverage (Lucie, Dogo, Valentin, Emile, & Mbacké, 2012; Ibrahim, Mohammed, Isah, & Aliyu, 2014). Outlined as follows are the pharmacological activities of the plant reported at the time of writing.

Antibacterial Activity

Antibacterial activity was investigated using the zone of inhibition method where the inoculated bacteria were cultured on agar and discs with the crude extract of *A. obesum* obtained from the stem-bark was used (Adamu et al., 2005; Chusri et al., 2014; Hossain et al., 2014a; Hossain et al., 2014b; Tijjani et al., 2011). When only the extract was used, strong inhibitory activity was observed against *Proteus mirabilis* and *Pseudomonas aeruginosa* (Akbar & Al-Yahya, 2011; Hossain et al., 2014a; Versiani et al., 2014). However, when combining the plant extract and a few selected antibiotics, strong inhibition could be seen against the majority of the clinical bacterial isolates. More significant inhibition could be seen against Gram-positive bacteria, suggesting that they were more susceptible, compared to Gram-negative bacteria (Chusri et al., 2014; Ramawat & Merillon, 2010; Tijjani et al., 2011; Versiani et al., 2014). The increased sensitivity of Gram-positive bacteria towards the drug synergism could be linked to the inhibition of the efflux pumps of the Gram-positive pathogens that affect the outer membrane permeability of the bacteria (Chusri et al., 2014). A number of alkaloid compounds isolated from the plants of the Apocynaceae family were shown to potentiate the activity of antibiotics (Hossain et al., 2014b; Tijjani et al., 2011). Tijjani et al. (2011) has tested the synergistic activity of *A. obesum* extract and oxytetracycline against several clinical bacterial isolates and the results are summarised in Table 1 and 2.

Table 1
Minimum inhibitory concentration (µg/ml) of antibiotic, A. obesum *extract and antibiotic* + A. obesum *extract needed to prevent visible growth of selected microorganisms (Tijjani et al., 2011)*

	Test organisms	Minimum inhibitory concentration (µg/ml)		
		Oxytetracycline	*Extract*	*Extract + Oxytetracycline*
Gram-negative	*Escherichia coli*	125	500	62.5
	Klebsiella pneumonia	1500	2000	1500
	Pseudomonas aeruginosa	500	1000	125
	Salmonella typhi	1000	1000	500
Gram-positive	*Bacillus subtilis*	500	1000	62.5
	Streptococcus pyogenes	500	500	125
	Staphylococcus aureus	1250	1250	125
	Corynebacterium ulcerans	1000	1250	500

Table 2
Zone of inhibition by antibiotic, A. obesum *extract and antibiotic* + A. obesum *extract (Tijjani et al., 2011)*

	Test organisms	*Zone of inhibition (mm)*		
		Oxytetracycline	*Extract*	*Extract + Oxytetracycline*
Gram-negative	*Escherichia coli*	25	20	27
	Klebsiella pneumonia	6	0	0
	Pseudomonas aeruginosa	20	18	24
	Salmonella typhi	17	19	24
Gram-positive	*Bacillus subtilis*	27	25	32
	Streptococcus pyogenes	29	26	37
	Staphylococcus aureus	26	26	30
	Corynebacterium ulcerans	21	19	26

Antiviral Activity

A. obesum extracts showed to reduce titre of the influenza A/PR/8/34 (or commonly known as the H1N1) virus (Kiyohara et al., 2012; Nagai et al., 1995). This might be attributed to the presence of the secondary metabolites such as anthocyanin glycosides and cardiotonic glycosides, which are both steroids. Through open silica gel column chromatography, it could be confirmed that the active compound responsible for the reduction of the virus is oleandrigenin-β-D-glucosyl (1,2,3,4)-β-D-digitalose, which is a cardiac glycoside (Hossain et al., 2014a; Nagai et al., 1995; Zu et al., 2012). The antiviral activity of *A. obesum* extract was proven by utilising Madin-Darby canine kidney (MDCK) cells infected with the virus. The methanolic extract of aerial parts of the plant was used in the study. Results showed that the plant extract reduced viral sialidase activity, and significantly decreased cell viability after the cells were exposed to the plant extract (Kiyohara et al., 2012). These results are presented in Table 3. The findings suggest considerable cytotoxicity from the usage of the plant extract for the treatment of viral infections. Hence, an optimum dosage of the extract needs to be carefully considered.

Table 3
Anti-influenza virus activity of A. obesum *extract as compared to the standard antiviral drug (Kiyohara et al., 2012)*

Compound tested	*Virus titre (% of control)*	*Cytotoxicity against MDCK cell (%)*
Adenium obesum extract	0.7	49.2
Control (water)	100	0
Zanamivir	0.3	4.1

Anticancer Activity

An abnormal hedgehog/GLI signalling pathway has been proven to be a foundation for the rapid expansion of tumours (Arai et al., 2011). Methanolic extracts of *A. obesum* prevented the progression of the signalling cascade, hence hindering the proliferation of pancreatic cancer (PANC1) cells (Arai et al., 2011; Farah et al., 2016). The target proteins which were inhibited were PTCH and BCL2. Cytotoxicity of *A. obesum* was also seen in other cancer cell lines such as breast (MCF-7), liver (HEPG2) and cervical (HeLa) (Almehdar et al., 2012; Ebrahim et al., 2013). This could be attributed to the presence of five active compounds which consist of four glycosides (cardenolides somalin, hongheloside A, 16-acetylstrospeside and honghelin) and one flavonol (3,3'-bis(*O*-metyl)quercetin) (Pengelly, 2004; Versiani et al., 2014).

Furthermore, the plant toxicity could be linked to excess production of reactive oxygen species (ROS) induced by the five active compounds mentioned (Farah et al., 2016). ROS is reported to be capable of inducing mitochondrial damage, apoptosis, oxidative stress and changes of DNA, causing damage to the genome (Hossain et al., 2014a). Further studies suggested that 3β-*O*(β-D-monoglycosidic) compounds with the cardenolide skeleton were most adept in inducing cytotoxicity (Bai et al., 2007; Versiani et al., 2014). Although *A. obesum* extracts was found to inhibit cancer cell growth effectively, however evidence suggested that it was also cytotoxic to normal cells. Almehda et al. (2012) tested the cytotoxic activities of *A. obesum* on various cell lines and the results are summarised in Table 4. In the study, three human cancer cell lines, namely, MCF7, HEPG2 and HeLa cells, together with human normal melanocytes (HFB4) were used. Sulforhodamine B colorimetric assay was used to evaluate the extract's cytotoxic effect. Doxorubicin, a well-known anticancer drug, was used as positive control. Half maximal inhibitory concentration (IC_{50}) for the extract was calculated from the optical density values resulting from the colorimetric assay.

Table 4
Cytotoxic activities of A. obesum *methanolic extract and its fractions on various cell lines (Almehda et al., 2012)*

Crude/Fraction of extract	*Half maximal inhibitory concentration, IC_{50} (μg/ml)*			
	MCF7	*HEPG2*	*HeLa*	*HFB4*
Crude	11.6	18.7	6.9	5.2
Petroleum ether	12.7	23.1	13.7	21.9
Chloroform	3.15	4..78	3.15	7.01
Butanol	3.56	4.17	3.15	3.96

According to Newman et al. (2008), cardiac glycosides of *A. obesum* could be used as effective therapeutic anticancer agents, especially when comparing their effect to contemporary anticancer medications which have toxic side effects, making this plant a potential alternative medicine for cancer treatment. On the other hand, pregnanes were cytotoxic against P388 murine leukemia cell lines. Pregnanes, with a l6-ene-20-one system, were found to be cytotoxic against adriamycin- and vincristine-resistant P388 cells. These pregnanes were also effective against adriamycin- and vincristine-sensitive P388 cells. However, pregnanes with no unsaturation at the C-16/C-17 position were not cytotoxic, indicating that the presence of a conjugated system involving the C-20 ketone group in pregnane is important for the cytotoxic activity (Nakamura et al., 2000). Previous research showed that betulin possessed cytotoxic effect on the BT-549 breast cancer cell line, which might serve as a potent agent in cancer medications. The results showed that betulin inhibited cancer cell proliferation with an IC_{50} value between 4.3-4.9 µg/mL (Šiman et al., 2016).

Immunomodulation

Previous studies have identified the *A. obesum* as a plant capable of enhancing the immune system. Increase in the concentrations of the ethanolic plant extract led to an increase in the white blood cell count especially the lymphocytes (Abalaka et al., 2012; Versiani et al., 2014). The ethanolic extract enhanced B and T cell proliferation through the synthesis of IgM (Ramawat & Merillon, 2010; Versiani et al., 2014). There were no signs of hepatotoxicity from this extract (Abalaka et al., 2012; Arai et al., 2011), and no indication of toxicity on prolonged usage. The dose used was very minimal, lower than the median lethal dose (LD_{50}) of 5000 mg/kg. Previous studies suggest that presence of the antioxidative secondary metabolites of the plant prevented oxidative damage and counteracted the toxicity induced by the plant (Pengelly, 2004; Ramawat & Merillon, 2010). Thus, the plant may be safe for oral consumption. However, the study has been conducted on Wistar rats and further toxicity studies should be conducted in clinical trials (Abalaka et al., 2012).

Other Therapeutic Benefits

Other studies have also reported that the plant possessed antimalarial and antitrypanosomal activities (Abdel-Sattar et al., 2009; Atawodi et al., 2002; Versiani et al., 2014). Reports suggested that all plant extracts from the petroleum ether, chloroform methanol and aqueous fractions showed inhibition of the *Trypanosoma brucei brucei* parasite. The active compound which showed antiparasitic activity was botulin, which is a triterpene (Ibrahim et al., 2014; Ramawat & Merillon, 2010). For the study of the antimalarial activity, human lung fibroblasts (MRC-5) infected

with the parasite were used. The cells were also used in testing the cytotoxicity of the extract; and the results indicated that the extract's toxicity was low (Abdel-Sattar et al., 2009).

CONCLUSION

A. obesum is commonly used as an ornamental plant in the Asian regions while in the African and Arabian Peninsula, this plant is used as a form of traditional medicine. To date, approximately 50 chemical compounds have been isolated from the plant, exhibiting a wide variety of effects including anticancer, antibacterial and antiviral properties, all which are promising and warrant further investigation.

FUTURE DIRECTION

To date, only chemical compounds from the moderately polar fractions from *A. obesum* have been documented, while the non-polar and the highly polar fractions have been given little attention. Hence, extraction using various solvents from low to high polarities are needed to isolate a wide range of compounds from the plant. Furthermore, the biological activities tested for *A. obesum* are limited. Most studies are focused on its antimicrobial and anticancer effects. Hence, more research should be conducted to explore the plant's effect on emerging diseases that lack effective treatment such as neurodegenerative and metabolic diseases.

The entire plant as a whole is toxic as it contains very high concentrations of cardiac glycosides. Utilisation of drug modification and synthesis technologies to overcome the toxicity issue of the compounds could be explored. On the other hand, isolation and identification of the bioactive compounds are essential. Investigation on the mechanism of action of each of the active compound is also important to aid in better understanding of the effects of the compound.

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