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Medicinal herbs and antioxidants: potential of *Rhinacanthus nasutus* for disease treatment?

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Abstract This review covers the biological activities of the medicinal herb, *Rhinacanthus nasutus,* which is part of the Acanthaceae family. This herb and the compounds isolated from it have the potential to be used for the treatment of a vast array of diseases, including neurological, (such as Alzheimer's, Parkinson's and depression), viral and bacterial infections (such as hepatitis and herpes virus), skin disorders, and control sugar levels in diabetic patients. Many diseases involve oxidative stress, particularly neurological diseases, where oxidative stress leads to neurodegeneration. Medicinal herbs such as *R. nasutus* appear to be effective at protecting against such oxidative stress. Herein we discuss the potential mechanisms by which they have their antioxidant effects, and their effects on other cellular pathways, which are involved in various disease states.

Keywords Oxidative stress · Reactive oxygen species · Traditional medicine · Natural products

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Abbreviations

AFB1	Aflatoxin B1
HSV	Herpes simplex virus
8-OHdG	Hydroxydeoxyguanosine
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MPO	Myeloperoxidase
$NO^{\cdot}$	Nitric oxide
PM	Plasma membrane
PGE_2	Prostaglandin E_2
GSH	Reduced glutathione
SOD	Superoxide dismutase
UV	Ultraviolet
VZV	Varicella-zoster virus

The plasma membrane (PM) is a vital organelle, which not only encloses the other organelles but also serves as a signaling platform allowing extracellular signaling molecules to interact with the target cells causing a cellular response. Lipids and proteins make up the major biological components of the PM and as the activity at the membrane increases as does the content of proteins. These lipids and proteins in the PM and other cellular molecules such as DNA are particularly susceptible to damage by reactive oxygen species (ROS) (Bokov et al. 2004; Devasagayam et al. 2004) such as hydrogen peroxide, superoxide or hydroxyl radicals (Table 1). Lipid peroxidation occurs when

lipids from the plasma membrane interact with any of the ROS, which results in a damaging chain reaction giving rise to toxic byproducts, which can act as second messengers away from the initial site of attack by the ROS (Kamat et al. 2000). Lipid peroxidation is a result of the ROS removing a hydrogen atom from a methylene group (CH_2) resulting in an unpaired electron ($^{\cdot}CH$). A molecular rearrangement stabilizes the carbon radical, which can then interact with an oxygen molecule to form a lipid peroxyl radical ($LOO^{\cdot}$). These lipid peroxyl radicals themselves are able to abstract hydrogen radicals, thus further potentiating the lipid peroxidation chain reaction. The harmful chain reaction of lipid peroxidation may be terminated by antioxidant molecules such as Vitamin E (Devasagayam et al. 2004). ROS damage to DNA occurs when free radicals such as $^{\cdot}OH$ react with the bases of the DNA molecule which can result in addition or loss of bases giving genetic mutations. The pyrimidine molecule of DNA is particularly susceptible to damage by ROS producing oxidative products such as 5-hydroxydeoxyuridine and 5-hydroxydeoxycytidine, the purines also interact with $^{\cdot}OH$ resulting in 8-hydroxydeoxyguanosine (8-OHdG) which has been implicated in carcinogenesis (Karihtala et al. 2011).

Reactive oxygen species are produced as a natural part of cellular life in the production of ATP from ADP in the mitochondria and fulfilling roles such as signal transducers (cytokine production, gene regulation or interleukin stimulation for leukocyte involvement) or providing protection against pathogens (Bickers and Athar 2006; Brimson and Nigam 2013; Devasagayam et al. 2004). The levels of ROS are kept in check by a number of mechanisms including enzymes, which break down or neutralize ROS (such as superoxide dismutase (SOD) and glutathione reductase) or antioxidants (such as vitamins C and E or reduced glutathione), which negate the harmful effects of the ROS (Scholz et al. 1989). Other non-enzymatic forms of antioxidants include carotenoids, flavonoids and related polyphenols, α-lipoic acid, etc. Oxidative stress is a state of oxidative damage to a cell or tissue resulting from a loss of control of ROS, which can lead to inflammation and cell death via apoptosis and necrosis (Behl et al. 1997a, b; Bokov et al. 2004; Fukui et al. 2009; Heo and Lee 2004; Ishige et al. 2001; Murphy et al. 1989; Patel and Chu 2011). Recently, our group demonstrated that certain Thai plant extracts with high total phenolic and flavonoid contents and antioxidant property could protect against UV-induced DNA damage and cytotoxicity in human keratinocytes (Thongrakard et al. 2013).

Table 1 A selection of reactive oxygen species, and their properties

Reactive species	Notation	Half life	Notes
Superoxide	$O_2^{\cdot-}$	10^{-4} s	Defense mechanism and byproduct of respiration
Hydroxyl radical	$^{\cdot}OH$	10^{-9} s	
Hydrogen peroxide	H_2O_2	Stable	Signaling molecule
Nitric oxide	$NO^{\cdot}$	1 s	Neurotransmitter

The decline related to aging and age related disease appears to correlate with the defects accumulated in metabolic pathways and the accumulation of ROS. The "free radical theory of aging" originally put forward in 1956 by D. Harmen, suggests that aging is the result of the accumulation of damage to macromolecules with in the cell caused by free radicals produced during metabolism (Harman 1956). One of the major sources of free radicals is the production of ATP by the mitochondria; whilst ATP production is a vital process for the cell, the ROS production appears to be detrimental to the mitochondria itself, which led to the expansion of the "free radical theory of aging" to the "mitochondrial theory of aging" (Harman 1972; Sastre et al. 2000). Strong evidence for the mitochondrial/free radical theory of aging is provided by studies in caloric restriction, which have shown that a decrease in calorie intake (without malnutrition) significantly reduces the production of ROS by the mitochondria, reducing mitochondrial damage, and increased the lifespan of the test animals (Barja 2002; Gredilla and Barja 2005; Merry 2004). Furthermore, caloric restriction has been shown to be beneficial in animal models of brain damage from excitotoxicity and metabolic insults (Bruce-Keller et al. 1999).

Although, for many years becoming widely accepted and much research being directed at antioxidants for the treatment of ageing and age related disease, these theories are not with out criticism including recent research in yeast, rodents and humans, which suggest that ROS is not the primary

or initial cause of aging, much of which has been recently reviewed by Hekimi et al. (2011). A large number of clinical trials have shown that antioxidants have failed to stop disease, and in some cases had detrimental effects to patients resulting in the early cessation of several studies (Howes 2006). It should also be noted that in certain circumstances antioxidants may act as pro-oxidants, such as ascorbic acid (vitamin C) in the presence of ferric iron is able to potentiate the peroxidation of lipids (Bernotti et al. 2003; Marcil et al. 2011), and the observation that β-carotene can increase the risk of lung cancer in smokers (Mayne et al. 1996).

Despite Howes' claim (Howes 2006) that the "Free radical Theory of aging is Dead" there is still much evidence that antioxidants can play a role in disease treatment, since there are many diseases that have a free radical element causing detrimental effects to the cells. Whether free radicals are the initial cause or a result of the disease, pharmaceuticals that can help regulate free radical homeostasis could be the key to managing and treating a number of conditions. Medicinal herbs and the compounds purified from the extracts could have the potential to provide the protection and possibly treatment of diseases, which have a ROS component.

Throughout history medicinal herbs and natural products have been used as remedies for many ailments, and cures for illnesses. Self prescribed remedies and herbal preparations are still used throughout the world for a range of ailments, such as anxiety, arthritis, headaches, insomnia and constipation (Craig 1999; Palasuwan and Soogarun 2005). In much of the world modern technology and innovations in pharmaceutical sciences has surpassed the traditional medicines, which once dominated the world of pharmacy (Gallo and Sarachine 2009). However, it should not be forgotten that many modem medicines have origins in plant extracts, such as *Rauwolfia serpentina* which gave rise to Reserpine (used for the treatment of high blood pressure), the foxglove (*Digitalis purpurea*) provided digitalis (a heart stimulant) and willow bark (*Salix alba*) has given us salicylic acid (the precursor to aspirin). Humans continue to suffer from a number of diseases caused by drug resistant microbes and parasites, as well as diseases to which modern medicine has yet to provide an effective cure such as Alzheimer's disease and various cancers. Attention in recent years has returned to the potential benefits of natural products and herbal medicines, or their natural metabolites for potential new pharmaceuticals. Much attention has been given to the antioxidant properties of these herbs (Palasuwan and Soogarun 2005), as well as the potential chemo preparative properties of metabolites such as ursolic acid, and cardio-protective properties (Gallo and Sarachine 2009; Kaewthawee and Brimson 2013).

With the number of species of plants disappearing at an alarming rate (Pimm and Raven 2000) it is vital that we document and conserve as many plants as possible, such that we do not miss out on a potential cure for an up-to-now incurable disease. Herein we review the potential of the medicinal herb from the Athracanthae family, *Rhinacanthus nasutus,* for the treatment of a range of diseases, with relation to ROS.

Rhinacanthus nasutus (L.) Kurz (Acanthaceae) (*R. nasutus*) (Fig. 1) is a medicinal herb native to Thailand and Southeast Asia, which is well known for its antioxidant properties. Traditionally the roots of *R. nasutus* have been used to treat snakebites, contributing to its common name 'snake jasmine'. The leaves and roots can also be boiled up into a tea, or made into a balm for the treatment of a range of diseases including ringworm or inflammatory disorders.

The potential therapeutic properties of *R. nasutus* are wide ranging, as well as having antibacterial, antifungal, antiviral and anti-parasitic activity (Kamaraj et al. 2010; Kernan et al. 1997; Kodama et al. 1993; Nadu 2009; Sendl et al. 1996), recent research from our laboratory has shown *R. nasutus* extracts

Fig. 1 Photograph of *Rinacanthus nasutus;* flowers and leaves

(and compounds isolated such as lupeol, stigmasterol and β-sitosterol as depicted in Fig. 2) to have potential neuroprotective properties, protecting mouse hippocampal cells (HT-22) against hypoxia (Brimson and Tencomnao 2011), and the toxic effects of glutamate and β-amyloid protein (Brimson et al. 2012). The mechanism by which these cells are protected is thought to involve the reduction of oxidative stress, as in both studies treatment with the *R. nasutus* root extract resulted in the reduction of intracellular ROS. However, whether this reduction was a direct result of the antioxidant compounds found within *R. nasutus* or a result of signaling from other compounds remains to be fully concluded. The protective effects of *R. nasutus* have also been shown in the livers of rats exposed to Aflatoxin B1 (AFB1), which causes toxicity to the liver (Shyamal et al. 2010). AFB1 was shown to reduce the levels of the natural cellular antioxidant; reduced glutathione (GSH), in male Wistar albino male rats and *R. nasutus* was able to prevent this reduction. Furthermore lupeol, which can be isolated from *R. nasutus*, has been shown to have similar protective and antioxidant maintaining effects (Preetha et al. 2006). GSH is a potent endogenous intracellular antioxidant neutralizing free radicals and ROS (Scholz et al. 1989) created in the production of ATP (Hughs 1964). This control of antioxidant levels can be applied to the experiments in the mouse hippocampal cells, since glutamate competes for the glutamate cysteine antiporter, leading to an imbalance in the homeostasis of cysteine, which is the precursor of glutathione (Behl et al. 1992; Schubert et al. 1992). The control of GSH levels in the brain has recently been shown to be particularly important in the underlying pathophysiology of a number of neurological disorders such as bipolar disorder, major depression and schizophrenia (Gawryluk et al. 2011). Recent work concerning diabetes has shown that *R. nasutus* is able to restore the levels of glutamate dehydrogenase in diabetic rats (Visweswara Rao et al. 2013), this may also be central to the protection of neuron cells against glutamate toxicity. If *R. nasutus* is able to modulate (or at least prevent the reduction of) GSH, as is alluded to by Shyamal's work (Shyamal et al. 2010) and to a certain extent the work we have carried out on HT-22 cells (Brimson et al. 2012), that would mean there is a potential of a therapeutic agent for bipolar disorder, major depression and schizophrenia. Furthermore, as *R. nasutus* has been shown to be neuroprotective and hepatoprotective possibly through an antioxidant mechanism, it has a potential for the treatment of diseases such as Alzheimer's disease or Parkinson's disease, which have an oxidative stress component.

There is already a president for the potential for the treatment of major depression with compounds that can be isolated from *R. nasutus* and various other medicinal herbs, as well as crude whole extracts of herbs themselves (Kulkarni et al. 2009; Moinuddin et al. 2010; Park et al. 2010; Subarnas et al. 1992). There have been several in vivo studies into the antidepressant effects of β-amyrin (Fig. 2), (Aragão et al. 2006; Subarnas et al. 1992, 1993a, b), which as a triterpene compound found in extracts of *R. nasutus* along with an array of similar structured compounds (Brimson et al. 2012; Nirmaladevi and Padma 2010; Rao 2010; Wu et al. 1995). Two studies in particular show that doses of β-amyrin (5–10 mg/kg) are capable of reducing immobility time in the forced swim test (a test that has been effective at identifying clinically effective antidepressants) in rats (Subarnas et al. 1993a), and that these effects are mediated through interactions with the GABA-A receptor, and also causes an increase in noradrenergic activity (Aragão et al. 2006).

There have been various other studies into the pharmacological properties of *R. nasutus*, including investigations into the inflammatory response to lipopolysaccharide (LPS) in RAW264.7 macrophage like cells. Napthaquinone derivatives isolated from *R. nasutus* leaves (Fig. 3) were found to concentration dependently reduce the release of nitric oxide ($NO^{\cdot}$) and prostaglandin E_2 (PGE_2) (Tewtrakul et al. 2009a). This reduction in $NO^{\cdot}$ and PGE_2 was shown to be a result of the down regulation of iNOS and prostaglandin-endoperoxide synthase 2 (COX-2). The effects of these napthaquinone derivatives on TNF-α were also investigated with no effect being identified. An earlier study using water and ethanol extracts of *R. nasutus* with a different cell line (J774.2 mouse macrophages) showed contrasting results, with *R. nasutus* unable to modulate iNOS and NO production alone, although *R. nasutus* did appear to be able to potentiate the $NO^{\cdot}$ inducing effects of LPS and cause a modest increase in TNF-α (Punturee et al. 2004). A more recent study suggests that *R. nasutus* may have both $NO^{\cdot}$ stimulating and inhibiting actions; using RAW264.7 macrophage cells, the study showed that the n-butanol fraction of the methanol extract induced $NO^{\cdot}$

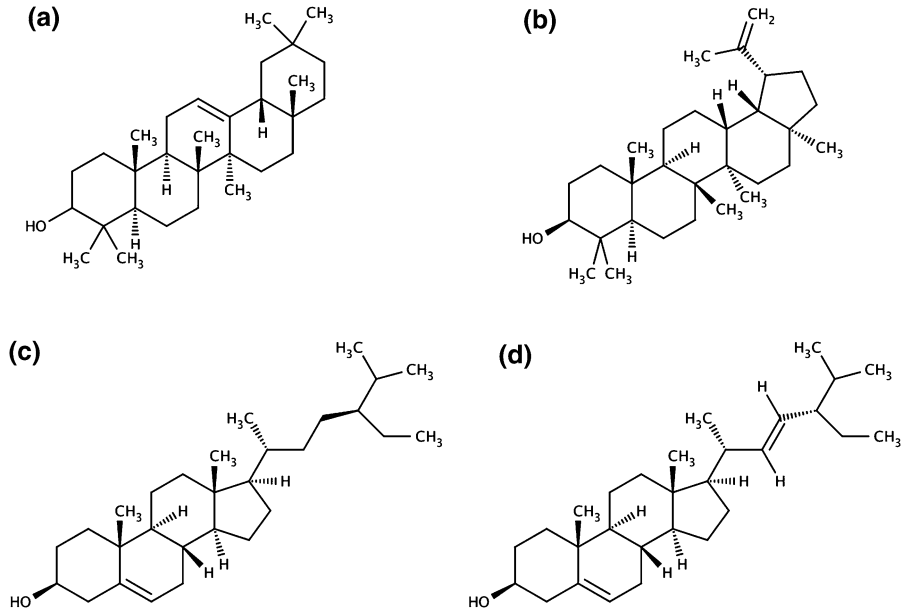

Fig. 2 Structures of **a** β-amyrin, **b** lupeol, **c** β-sitosterol, **d** stigmasterol

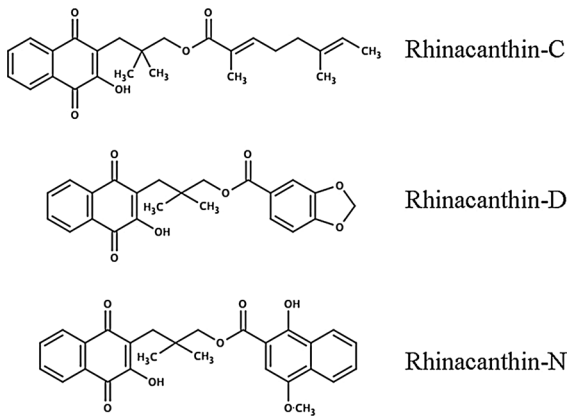

Fig. 3 Napthaquinone derivatives isolated from Rn leaves isolated by Tewtrakul et al. (2009a)

production, conversely *R. nasutus* was also able to inhibit LPS induced $NO^{\cdot}$ (Horii et al. 2011).

Despite the napthaquinone derivatives not being able to affect TNF-α, in RAW264.7 macrophage like cells (Tewtrakul et al. 2009a), the napthaquinone derivatives have been shown to dose dependently modulate antigen induced TNF-α, IL-4 mRNA expression in RBL-2H3 cells (Tewtrakul et al. 2009b). Also it has been shown that *R. nasutus* extracts are able to protect HaCaT Keratinocytes against apoptosis induced by the pro-inflammatory cytokines IFN-γ and TNF-α (Thongrakard and Tencomnao 2010). Large quantities of ROS are released during the inflammatory process, which is involved in destroying invading organisms and or degrading damaged structures, also ROS has been shown to induce apoptosis in keratinocytes via a mitochondrial modulating mechanism (Bickers and Athar 2006). Furthermore, the immuno-modulatory effects of *R. nasutus* (water and ethanol extracts) have been shown, with treatment of human peripheral blood mononuclear cells (PBMCs) showing an increase in proliferation in response to mitogens (Punturee et al. 2005). The Punturee et al. (2005) study also showed that the water and ethanol extracts could significantly increase IL-2 and TNF-α production in PBMCs when co-stimulated with mitogen. They also showed that *R. nasutus* extracts were able to increase secondary antibody production in vivo, using mice treated with BSA.

The use of *R. nasutus* is not limited to immunological and neurological aspects of disease; there has been much study into the use of *R. nasutus* extracts with respect to cancer treatments. The rhinacanthins C and N (Fig. 3) as well as other rhinacanthin compounds (such as rhinacanthin G, O, M and Q) have been shown to produce anti-proliferative effects in vitro in amongst others, HeLaS3 cells (Siripong et al. 2006, 2009) PC-3 and T24 cells (Gotoh et al. 2004), human leukemia CCRF-CEM cells and the multidrug-

resistant CEM/ADR5000 (Siriwatanametanon et al. 2010), KB (human epidermoid carcinoma) (Kongkathip et al. 2004) Hep-2, MCF7, HEP-G2, SiHa, and colon 26-cells (Siripong et al. 2006). Furthermore there have been some studies in vivo studies showing that *R. nasutus* extracts and rhinacanthin compounds can reduce tumor size in mice implanted with sarcoma cells (Gotoh et al. 2004; Siripong et al. 2006). The studies in vitro have shown that rhinacanthone, isolated from *R. nasutus*, is able to induce apoptosis in HeLa cells via several mechanisms, including the increase in the pro-apoptotic protein Bax and decrease in the anti-apoptotic proteins Bcl-2 and survivin, as well as the subsequent activation of caspases 3 and 9 (Siripong et al. 2009). Siripong et al. (2009) further showed the involvement of the mitochondria in the *R. nasutus* induced apoptosis, with apoptosis-inducing factor (AIF) translocating from the mitochondria to the nucleus.

Finally with regard to *R. nasutus*, it is thought to be useful in the treatment of diabetes; and is often used as such in traditional folk medicine (Wu et al. 1988). Two recent studies in rats have provided evidence that *R. nasutus* could be effective at treating diabetes, the authors show that blood glucose, and body weight of rats treated with streptozotocin can be returned to normal after treatment with *R. nasutus* (Rao and Naidu 2010). Further study with *R. nasutus* and streptozotocin treated rats has identified that *R. nasutus* can reduce lactate dehydrogenase (LDH) in diabetic rats (Visweswara Rao et al. 2013) (increased LDH in diabetes is associated with reduced insulin secretion (Singh et al. 2001)), and restore glucose-6-phosphate dehydrogenase G6PDH (Visweswara Rao et al. 2013), which has been shown to be reduced in diabetes. It may be possible that the hypoglycemic effect could be the result of β-sitosterol and stigmasterol, since they have previously been shown to synergistically reduce blood glucose levels (Jamaluddin et al. 1994). There are other possible explanations for the hypoglycemic effect of *R. nasutus*, such as the rhinacanthin molecules found within. The 1,4-naphthoquinones (a group of molecules to which the rhinacanthins fall with in) have recently been investigated for their ability to activate the insulin receptor (He et al. 2011), although the rhinacanthins found in *R. nasutus* have not been individually tested for this effect it remains a possibility. The oxidative damage to the vascular system in diabetes can be reduced by *R. nasutus* (Rao et al. 2012). The oxidative stress as a result of lipid peroxidation can produce methane dicarboxylic aldehyde, which plays a role in the progression of diabetes (Mancino et al. 2011) by altering the fluidity gradient of the membrane, therefore possibly inhibiting receptor and enzyme activity. The recent study has shown that *R. nasutus* can reduce the lipid peroxidation seen in streptozotocin treated rats, as well as return the levels of superoxide dismutase and catalase (two major free radical scavenging enzymes) to normal (Rao et al. 2012). Furthermore *R. nasutus* treatment of the streptozotocin treated rats can return the levels of glutathione peroxidase, in the liver, to normal. Glutathione peroxidase functions to reduce lipid hydroperoxides as well as reduce hydrogen peroxide, when its substrate, GSH, is diminished glutathione peroxidase activity is reduced. It is likely that *R. nasutus* is preventing the levels of GSH from diminishing, as in the other studies previously mentioned, therefore providing protection against the oxidative stress caused by the streptozotocin in the livers of the rats.

As this review has shown, *R. nasutus* has the potential to be useful in the treatment of a vast number of diseases. The compounds that can be isolated from *R. nasutus* such as (although not limited to) lupeol, stigmasterol, β-sitosterol and β-amyrin warrant investigation into their cancer prevention and treatment, neuro, cardio, and hepato-protection properties as well as their roles in inflammatory diseases. The clinical studies already carried out with this herb in the treatment of viral infection from the herpes simplex virus and Varicella-zoster virus have been successful and it is of interest that *R. nasutus* and the compounds found within have the ability to protect cells from oxidative stress, particularly oxidative stress as is found in neurological diseases such as Alzheimer's disease, which currently has no cure. Further investigation into these herbal extracts is warranted to assess their potential as treatments for multiple diseases.

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