



Russelioside B: a Pregnane Glycoside with Pharmacological Potential

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Abstract

Pregnanes and pregnane glycosides or their esters are well-studied secondary metabolites, many of them exhibit immunomodulator, anticancer, antidiabetic, antarthritic, antiulcer, anti-nociceptive, hypolipidemic, anti-inflammatory, and antibacterial properties. Pregnane glycosides are widely distributed in the families Apocynaceae and Asclepiadaceae. Plant members of the genus *Caralluma* R.Br., Apocynaceae, are among the most studied species because of uses in traditional medicine or as food. They are a rich source of pregnane glycosides, as russelioside B. However, the bioactivity profile of this pregnane glycoside has not been reviewed until now. The present review aims to summarize the most important pharmacological and therapeutic applications of russelioside B with specific emphasis on the mechanism of actions associated with its administration in preclinical models. Russelioside B has many pharmacological effects including antidiabetic, anti-obesity, anti-nociceptive, antiulcer, anti-inflammatory, anti-arthritis effects, and antibiofilm, and wound healing activities. Despite its outstanding pharmacotherapeutic potential, russelioside B has never been tested in clinical trials. This review indicates that russelioside B is a potentially promising bioactive candidate, but further deeper mechanistic studies and clinical trials are needed in the future to elucidate its interaction with receptors of specific genes.

Keywords Pregnane glycoside · Structural formula · Therapeutic application · Pharmacological activity, Mechanism of action · Toxicity

Introduction

Medicinal plants and their phytoconstituents (natural products) are source for therapeutic applications and play a pivotal role in maintaining proper health for human beings and in controlling various diseases (Gurib-Fakim 2006). “Natural products” are chemical compounds that are isolated from living organisms such as plants, animals, fungi, microorganisms, marine organisms, and terrestrial vertebrates and invertebrates (Newman et al. 2000). Newman and Cragg published several reviews under the topic “Natural products as sources of new drugs,” covering the years 1981 to 2019 (Newman and Cragg 2007; Newman and Cragg 2012; Newman and Cragg 2016; Newman and Cragg 2020; Newman et al. 2003). The reviews

focus on the fact that many drugs in the market are derived from natural origin. The reviews revealed that, out of the 1328 new chemical entities approved as drugs between 1981 and 2016, only 359 were of synthetic origin and a little less than half of those new drugs (549, exactly) were from natural origin or natural product derivatives. Furthermore, out of 136 approved nonbiological anticancer compounds in the period (1981–2014), only 23 were of synthetic origin (*i.e.*, not derived from natural compounds nor natural derivatives) (Newman and Cragg 2016).

Over the past 20 years, the top pharmaceutical companies such as Merck, Pfizer, and Bristol Myers Squibb have declined the in-house research programs on natural products (Beutler 2009). This approach has been observed in the USA, while a few European and Japanese pharmaceutical companies continue to support research on natural product drug discovery (Atanasov et al. 2021; Thomford et al. 2018). Beutler (2009) has enumerated several reasons for this trend, (i) process of drug discovery from natural products is slow; (ii) all of the easy natural product drug discoveries have been made; (iii) synthesis of complex structure of natural products is difficult; (iv) maintaining continuous supply of natural

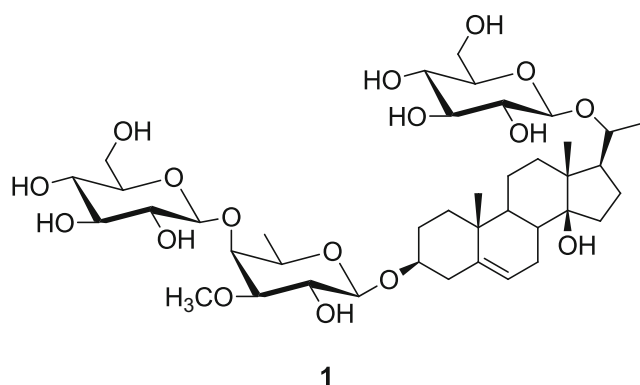
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products is difficult; (v) high throughput chemistry is viewed as better than natural products; and (vi) sometimes, natural product formula may not be patentable in the USA. Of the abovementioned reasons, search in natural products still holds out the best options for finding novel agents/active templates, which when worked on in parallel with chemists and biologists offer the potentials to discover novel structures with therapeutic activity against variety of human illnesses (Newman and Cragg 2020). In addition, natural products, mainly from plant sources, still provide and demonstrate important structural diversity, and showed a wide variety of novel and templates to the Western medicine (Balunas and Kinghorn 2005; Harvey 2008; Newman et al. 2003). Recent reports revealed the significance of natural products in health care system, providing that 80% of the world population still use plant-derived products (Butler 2008; Farnsworth et al. 1985). It is also reported that about 50% of all therapeutic drugs in clinical use are of natural origin, or their derivatives, or their analogs (Balandrin et al. 1993), and 74% of the most important drugs consist of plant-derived active ingredients (Arvigo and Balick 1993).

This review summarizes recently published studies on russelioside B (**1**), a major pregnane glycoside isolated from *Caralluma* species focusing on its biological and pharmacological activities.



Search Strategy

A systematic search in the literature was performed through Egyptian Knowledge Bank database, Google Scholar, J-Global, Scopus, Dr. Duke's Phytochemical and Ethnobotanical Databases, PubMed, Web of Science, and Elsevier databases. The search was done using all available MeSH terms for russelioside B, structure, isolation, solubility, bioavailability, uses, biological activity, toxicity, pharmacokinetics, clinical investigations, and mechanism. The article search time was from inception to the year 2021.

Discussion

Natural Sources

Russelioside B (**1**) was isolated from the following species: *Caralluma retrospiciens* (Ehrenb.) N.E.Br., syn. *C. russelliana* (Courb. Ex Brongn.) Cufod. *Boucerosia russelliana* Courbon ex Brongn.) (Abdul-Aziz Al-Yahya et al. 2000); *C. quadrangula* (Forssk.) N.E.Br., syn. *B. quadrangula*, Decne., *Ceropegia quadrangula* (Forssk.) Bruyns and *Monolluma quadrangula* (Forssk.) Plowes (Abdel-Sattar et al. 2016; Abdel-Sattar et al. 2017); *C. tuberculata* N.E.Br., syn. *Apteranthes tuberculata* (N.E.Br.) Meve & Liede, and *Borealluma tuberculata* (N.E.Br.) Plowes, and *Borealluma aucheriana* (N.E.Br.) Plowes (Abdel-Sattar et al. 2013); and, finally, *C. europaea* (Guss.) N.E.Br., syn. *C. negevensis* Zohary ex Feinbrun, *A. europaea* subsp. *negevensis* (Zohary ex Feinbrun) M.B. Crespo, and *A. negevensis* (D. Zohary) Plowes (Braca et al. 2002). The 20R isomer of **1** was isolated from *C. umbellata* Haw [Syn: *Stapelia umbellata* Roxb, *C. campanulata* N.E.Br.] (Ray et al. 2011); *C. indica*; *C. adscendens* var. *gracilis* Gravelly & Mayur (Reddy et al. 2011); and *C. pauciflora* (Wright) N.E. Brown (Gummadi et al. 2021). The summary of plants containing russelioside B, parts used (Fig. S1), and uses/biological activities is shown in Table S1.

Chemical Structure

Russelioside B (**1**) was first separated by our group from *C. russelliana* (Abdul-Aziz Al-Yahya et al. 2000) and later from *C. quadrangula* (Abdel-Sattar et al. 2016; Abdel-Sattar et al. 2017) and identified by LC-MS in *C. tuberculata* (Abdel-Sattar et al. 2013). It was isolated as colorless crystals, had the molecular formula $C_{40}H_{66}O_{17}$ as determined using ESI-MS (m/z 841 $[M + Na]^+$) data, and confirmed by its ^{13}C NMR (Abdul-Aziz Al-Yahya et al. 2000). It showed no UV activity and the IR (KB, cm^{-1}) spectrum showed strong absorptions at 3562 (OH alcohol), 2865 ($-C=C-$), and the absence of carbonyl groups. The presence of glucose and 3-*O*-methyl-6-deoxygalactose moieties was proved by acid hydrolysis and from detailed NMR analysis, which showed the presence of three anomeric protons and carbons (1H and ^{13}C NMR spectra). The linkages of sugar to aglycone and sugar to sugar were proved through HMBC correlations. The stereocenters of russelioside B structure was determined from the analysis of the NOESY correlations, and it was concluded that the side chain is oriented with carbon C-20 having the *S* configuration (Table S1). The russelioside B was elucidated as calogenin 20 (*S*)-*O*- β -D-glucopyranosyl-3-*O*-[β -D-glucopyranosyl-(1 \rightarrow 4)- β -D-(3-*O*-methyl-6-deoxy)] galactoside.

Physicochemical Properties

Russelioside B was isolated as colorless crystals with melting point of 202–204 °C, and had $[\alpha]_D^{25} - 15.4^\circ$. It is soluble in water, methanol, and ethanol and insoluble in chloroform and ether. Other physicochemical properties of russelioside B were predicted and reported by ChemAxon, viz. logP ($10^{-1.3}$ g/l), pKa (strongest acidic: 11.78), pKa (strongest basic: –3.2), and refractivity of $196.68 \text{ m}^3 \cdot \text{mol}^{-1}$ (https://chemaxon.com/products/calculators-and-predictors#logp_logd).

Quantification

Quantification of russelioside B was performed using LC-MS analysis in the methanolic extract of *C. tuberculata* (Abdel-Sattar et al. 2013). The analysis was performed on HPLC system of an Agilent 1200 system composed of solvent delivery module, quaternary pump, autosampler, and column compartment. The column effluent was connected with Agilent 6320 Ion Trap LC-ESI-MS. Analytes were separated on Agilent Zorbax SB-C18 (150 mm length \times 4.6 mm i.d., 3.5 μm). A volume of 1 μl from each standard or sample solution was injected 3 times for LC-ESI-MS analysis applying two-segment and positive mode. The developed method used 20% formic acid (0.1%) and 80% acetonitrile as eluting system and flow rate 0.5 ml/min over 25 min. Russelioside B (t_R 2.73 min) was determined along with russelioside C (t_R 4.53 min) and caratuberside C (t_R 17.57 min) in the methanolic extract of *C. tuberculata* from the corresponding calibration curve using the peak area of each m/z extracted (Abdel-Sattar et al. 2013). LC-MS analysis showed that russelioside B, russelioside C, and caratuberside C present in amounts of 239, 12.8, and 42.8 mg/g, respectively.

Biological Activity

Acute Toxicity (LD₅₀)

The toxicity of russelioside B (**1**) was carried out by determining its LD₅₀ in male albino mice. After acclimatization (5 days), the animals were fasted overnight prior dosing. A batch consisting of 10 male mice was administered with a single dose orally once with varied concentrations (500 up to 5000 mg/kg bw) of **1**, in parallel with control group. All the animals in all groups were observed for 15 days. Observations were made at least once during the first 30 min and every 4 h in the first day and once every day for the next 14 days. The results showed no signs of toxicity up to 5000 mg/kg body wt.

Anti-hyperglycemic Activity

Diabetes mellitus has emerged as a major public health problem worldwide, which is predicted to worsen in the coming decades,

particularly in developing countries. The global prevalence of DM among adults (aged 18–99 years) was estimated to reach 451 million people in 2017. These figures were expected to reach 693 million adults by 2045 (Cho et al. 2018). Nearly half of this figure remains with undiagnosed diabetes (type 2) and there was an estimated 374 million people with impaired glucose tolerance. In those who are diagnosed, diabetes control is not up to the maximum, which potentially increases the risk of associated complications, resulting in poor health outcomes. Approximately 5 million deaths globally were attributable to DM in the age of 20–99 range. In 2017, the global health expenditure on people with diabetes was estimated to be USD 727 billion (Atlas 2015). An alternative approach of the use of western medicine to treat diabetes mellitus is the use of various natural agents possessing hypoglycemic effect or their derivatives. Several species of the genus *Caralluma* are rich in pregnane glycosides and showed promising blood glucose-lowering effects of their extracts or their corresponding fractions, namely, *C. russelliana* (Zari and Al-Thebaiti 2018), *C. dalzielii* N.E.Br. (Tanko et al. 2012), *C. adscendens* var. *attenuata* (Wight) Grav. & Mayur. (Singh and Kori 2014; Venkatesh et al. 2003), *C. arabica* N.E.Br. (Radhakrishnan et al. 1999; Wadood et al. 1989), *C. edulis* (Edgew.) Benth. ex Hook.f. (Sayantan and Abhishek 2012; Wadood et al. 1989), *C. umbellata* Haw. (Kumar 2016), *C. tuberculata* N.E.Br. (Abdel-Sattar et al. 2011; Abdel-Sattar et al. 2013), *C. sinaica* (Decne.) A.Berger (Habibuddin et al. 2008), *C. adscendens* var. *fimbriata* (Wall.) Gravely & Mayur. (Latha et al. 2014), and *C. quadrangula* (Abdel-Sattar et al. 2017; Al-Adhrai et al. 2018).

Russelioside B (**1**) was evaluated in STZ-induced diabetic rats for its anti-hyperglycemic activity (15 and 25 mg/kg), alongside with the MeOH extract *C. quadrangula* and related fractions (CHCl₃, *n*-butanol and remaining water) (Abdel-Sattar et al. 2017). The effect of **1** on body weight, fasting blood glucose (FBG) level, serum insulin level, and hepatic glucose-6-phosphatase activity was measured. Compound **1** (25 mg/kg) recovered the body weight nearly comparable to that of glibenclamide (5 mg/kg), the reference drug. The administration of **1** at 25 mg/kg showed a significant decrease in fasting blood glucose level in diabetic treated rats similar to the effect of glibenclamide. Compound **1** (25 mg/kg) resulted in the decrease of fasting serum glucose (FSG) from 600.3 ± 33.96 mg/dl (diabetic control) to 322.66 ± 20.4 mg/dl. The treatment of diabetic rats with the various extracts and fractions and RB showed different activities on serum insulin level. The MeOH extract (200 mg/kg), CHCl₃, and *n*-butanol fractions (100 mg/kg) showed significant increase in the insulin levels in the diabetic treated rats, which is similar to that of glibenclamide, while **1** showed a moderate effect. On the other hand, the activity of gluconeogenic enzyme, G-6-Pase, was significantly increased in the diabetic rats compared to those in normal control. The MeOH extract (200 mg/kg), chloroform, *n*-butanol fractions (100 mg/kg), and RB (25 mg/kg)

showed significant reduction in hepatic G-6-Pase activity by about 51.1, 57.7, 51.8, and 54.8%, respectively.

Anti-hyperglycemic Mechanism of Action

The suggested mechanism of the anti-hyperglycemic activity of **1**, at least partly, may be due to stimulation of insulin secretion, inhibition of glucose-6-phosphatase activity, enhancement of glucose utilization, and inhibition of glucose absorption. The change in body weight was not strong in all tested fractions and **1**; this may be due to the effect of their pregnane glycosidic content which showed appetite suppressant activity (Abdel-Sattar et al. 2018).

In another study, compound **1** showed improvement effect on glucose metabolism in the liver of STZ-induced diabetic rats (Abdel-Sattar et al. 2016). The daily oral administration of **1** (50 mg/kg) for a period of 30 days resulted in the improvement of the FSG level, glycated hemoglobin percent, serum insulin level, and lipid profile. Administration of **1** showed a significant decrease in the levels of serum total glycerides, and atherogenic index with a significant increase in the level of high-density lipoprotein cholesterol when compared with the diabetic group. A significant improvement was also observed on the activities of glucokinase, glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, and glycogen phosphorylase enzymes in the liver of STZ-diabetic rats, the key player enzymes of carbohydrate metabolism. Furthermore, administration of **1** reverted gene expression of glucokinase, glucose-6-phosphatase, glycogen synthase, and glycogen synthase kinase-3 β to near-normal levels.

The hypoglycemic action of russelioside B (**1**) may have two mechanisms of actions; this pregnane glycoside may reduce the blood glucose level by decreasing the intestinal glucose absorption, or/and by stimulation of insulin secretion from the pancreas. Yoshikawa (2002) proposed that steroidal glycosides partially stay on the surface of the small intestine and lower glucose absorption, thus regulating the increase in blood glucose levels (Yoshikawa 2002). The decline in total glyceride (TG) and total cholesterol (TC) in russelioside B-treated diabetic animals could be due to the increase in insulin secretion potentiated by **1**. It was suggested that it also inhibits cholesterol biosynthesis and promoted the activity of lipolytic enzymes in hyperlipidemic animals (Sethi et al. 2007). The reduction of serum TG following treatment with **1** might also facilitate glucose oxidation. In addition, the increase in insulin secretion by RB is reflected by the rise in intracellular glycogen deposition particularly in liver tissues due to stimulation of glycogen synthase (GS) and inhibiting glycogen phosphorylase and GSK-3 β expression. Russelioside B (**1**) affects also hepatic glucose metabolism by increase of GK activity as well

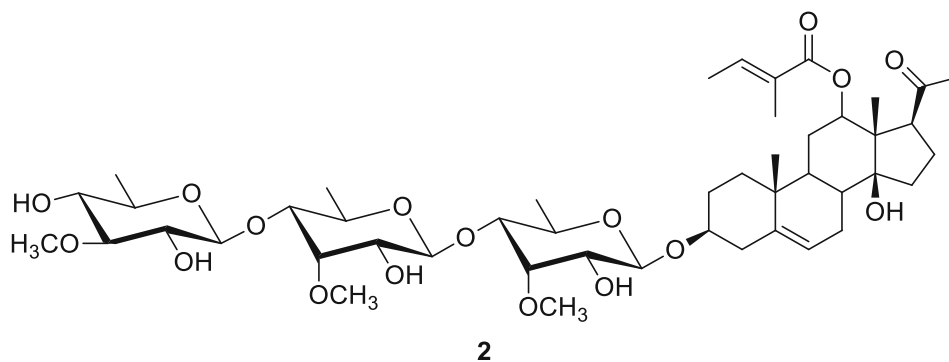
as its expression, which could be attributed to the increase in insulin concentration (Morinaga et al. 2008).

Anti-obesity Activity

Obesity and overweight have become a major common health problem globally, experiencing increasing rates in both developed and developing countries (Shao et al. 2014). In 2016, it was estimated that 1.9 billion adults were overweight and 650 million out of 1.9 billion overweight were classified as obese (Shuaib et al. 2021). The worldwide prevalence of obesity has nearly tripled between 1975 and 2016 (Abarca-Gómez et al. 2017).

In obesity, the imbalance between energy intake and expenditure results in excessive body fat accumulation. This may lead to serious non-communicable diseases, such as type 2 diabetes mellitus, hypertension, dyslipidemia, cerebro- and cardiovascular diseases, sleep apnea, and some cancers (Son and Kim 2020). The key strategy to control overweight and obesity is a combination of change in lifestyle and physical activity, in addition to the use of pharmacological therapy to prevent chronic positive impairments in the energy equation by elevating average daily metabolic rate and increasing energy expenditure (Schrauwen and Westerterp 2000). The pharmaceutical drugs for the control of obesity include the use of thermogenetic agents, lipase inhibitors and compounds that suppress appetite or stimulate the CNS (Shashoua and Hesse 1996), which may have undesirable harmful side effects.

Natural products (including crude drug, extracts, or isolated compounds) that induce body weight loss and prevent diet-induced obesity are widely consumed in control of the metabolic disorders (Hanl et al. 2005). Plants of genus *Caralluma* have long been used to control weight gain and as appetite suppressant, namely *C. fimbriata*, *C. attenuate*, *C. tuberculata*, *C. indica*, *C. stalagmifera*, *C. umbellata*, *C. lasiantha*, and *C. edulis* (Adnan et al. 2014). Commercial products containing *C. fimbriata* extract are available in the international markets. The use of *C. fimbriata* extract (100 mg/kg/day) showed significant weight loss and improved lipid profile as compared with hypercaloric diet control group in rats, resulting in suppressing appetite and preventing fat accumulation (Ambadasu and DSWRW, 2013). This effect is due to inhibition the formation of enzymes responsible for fat synthesis (Naingade et al. 2013). The appetite-suppressing effects of *C. fimbriata* have been ascribed to its content of pregnane glycosides (Adnan et al. 2014). This hypothesis was confirmed by the isolation of P57 (**2**), an oxypregnane steroidal glycoside isolated from *Hoodia gordonii* (Masson) Sweet ex Decne., Apocynaceae, a succulent plant consumed traditionally by the Khoi-San of South Africa and Namibia as a hunger and thirst suppressant (appetite suppressant) (Vermaak et al. 2011).



Caralluma quadrangula and *C. tuberculata*, the source of russelioside B (**1**), have been consumed by Bedouins of Saudi communities in cases of thirst and hunger and for the treatment of diabetes, and when food supplies were low. Abdel-Sattar and coauthors (2016) observed the failure of **1** to restore the fall in body weight in diabetic rats induced by STZ and was explained possibly by the appetite suppressant effect of pregnane glycoside (Abdel-Sattar et al. 2016; Liu et al. 2013; Tucci 2010; Vermaak et al. 2011). This observation encouraged the authors to investigate the possible appetite suppressant activity of RB. Abdel-Sattar and coauthors (2018) designed experimental protocol to examine the potential role of RB in controlling weight gain associated with high-fat (HF) diet in rats focusing on the influence of RB on adipose tissue expression for adipokines as well as energy expenditure. The assessment of the effect RB was carried out using male Wistar rats (fed on high-fat diet for 16 weeks) at two oral doses (25 and 50 mg/kg). Animal parameters like weight gain, blood glucose, serum lipids, and liver enzyme activities were measured, in addition to liver and adipose tissue indices. Adipose tissues were processed for histopathological examination (Fig. 1), and for measurement of mRNA expression of uncoupling protein-1 (UCP-1), visfatin, adiponectin, leptin, and carnitine palmitoyl transferase-1 (CPT-1). In addition, serum levels of insulin, interleukins (IL-1b and IL-6), tumor necrosis factor- α (TNF- α), adiponectin, resistin, and leptin were assessed. Fig. 1 shows tissue sections from the adipose tissues. The adipose tissue from HF diet control rats showed larger diameter for adipocyte spaces. Treatment with **1** (50 mg/kg) significantly reduced the diameter of the adipocyte spaces. The modulation of all these parameters confirmed the potential benefits of russelioside B (**1**) in diminishing weight gain and improving the inflammatory perturbations and energy expenditure in HF diet-fed rats.

Anti-obesity Mechanism of Action

This study confirmed the potential therapeutic benefits of russelioside B (**1**) in decreasing weight gain, improved lipid profile, and insulin resistance as indicated by the HOMA-IR index. The authors highlighted that RB regulated enzymes involved in carbohydrate metabolism in the liver of diabetic rats (Abdel-Sattar et al. 2016). Furthermore, the data revealed

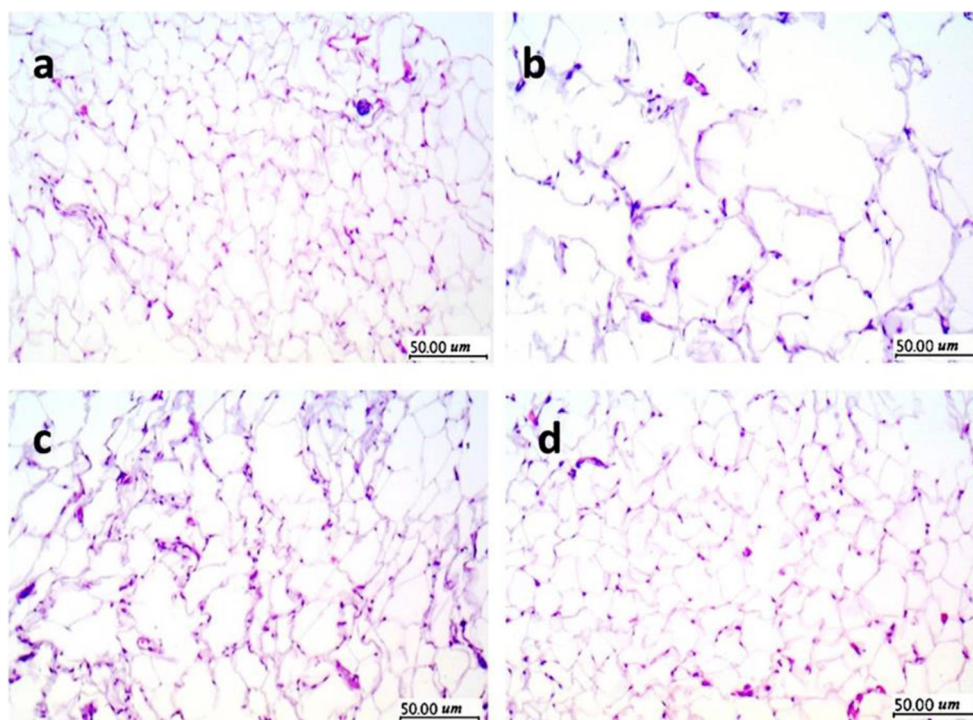
the upregulation of both UCP-1 and CPT-1 genes and increased their protein level in the brown adipose tissue in treated rats with **1**, which results in fatty acid β -oxidation, and activation of the brown adipose tissue (Gonzalez-Hurtado et al. 2018). This action leads to improve glucose homeostasis and modulate insulin resistance (Zaitone et al. 2015). The authors reported that the upregulation of UCP-1, in addition to CPT-1, plays a crucial role in controlling of obesity (Rameshreddy et al. 2018), through enhancement of lipolysis and decreased total glycerides. The released free fatty acids are transported to the mitochondria via the activated CPT-1 enzyme, with simultaneous induction of the thermogenic activity of UCP-1, which suggested to reduce visceral fat mass (Han et al. 2017).

The study also revealed the amelioration effect of russelioside B (**1**) on pro-inflammatory cytokines (IL-1B, IL-6, and TNF- α), adipokines (leptin, adiponectin, resistin, visfatin), and their mRNA expression in the pathology of insulin resistance. Interestingly, compound **1** elevated serum leptin, resistin, and visfatin, and reduced adiponectin levels. This led to suppression of appetite and improvement of thermogenesis, insulin sensitivity, and insulin resistance. Therefore, the overall anti-obesity action of **1** may be, at least partly, attributed to its anti-inflammatory and adipokine modulation, in addition to its beneficial effect on energy expenditure.

Antiparasitic Activity

Malaria and trypanosomiasis are vector-borne diseases caused by *Plasmodium* and *Trypanosoma* parasites, respectively. Both diseases continue to be the main reasons of community health problem for many millions of people in both tropical and subtropical zones of the world (Ashley et al. 2018). The recent malaria report (WHO 2020) considered almost half of the world's population was at risk of malaria infection; the number of malaria deaths increased up to 409,000; and approximately 229 million new malaria cases occurred in 2019 worldwide. On the other hand, human African trypanosomiasis (HAT) showed great decrease in the new cases in the last 10 years; however, there are more than 57 million people who still remain at risk from the disease in 36 countries (Kassebaum et al. 2016). Many

Fig. 1 Effect of russelloside B (**1**) on the diameter of adipocyte spaces in the lumbar adipose tissue. **a** Tissue section from normal rat adipose tissue showing low-diameter adipocyte space. **b** Tissue section from adipose tissue from high-fat diet control rats showing larger diameter adipocyte spaces. **c, d** Tissue sections from adipose tissues from high-fat diet-fed rats treated with **1** at 25 and 50 mg/kg, respectively. **e** Box plots showing the medians and quartiles for diameters (μm) of adipocyte spaces. *Significant versus normal group. #Significant versus high-fat diet control group. Comparison was performed by non-parametric ANOVA followed by Dunn's test at $p < 0.05$. Reproduced from Abdel-Sattar et al. (2018)



of the antiparasitic drugs currently in use showed serious toxicity and upsurge of drug resistance or a lack of adherence to treatment. Therefore, there is an urgent and global need to discover new effective drugs. The biological assays to discover new antiparasitic drugs from natural products showed great promise due to their efficacy and good selectivity (Kayser et al. 2003).

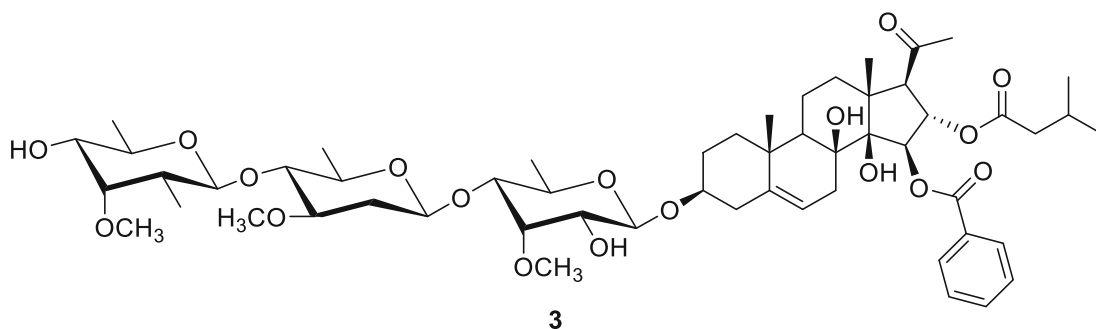
Abdel-Sattar and co-workers tested 42 Saudi plants and some fractions obtained thereof for their antiplasmodial and antitrypanosomal activity. Among these plants, *C. tuberculata* showed some moderate activity against chloroquine-resistant

strain (K1) and sensitive strain (FCR3) of *Plasmodium falciparum*, and against *Trypanosoma brucei brucei* GUTat 3.1 strain. Application of biologically guided fractionation approach on *C. tuberculata* methanolic extract led to isolation of six pregnane glycosides from the moderately active chloroform fraction (Abdel-Sattar et al. 2008). Five compounds showed weak antimalarial activity against *Plasmodium falciparum* (K1, drug resistant) with $\text{IC}_{50} < 12.5$ and > 6.25 $\mu\text{g/ml}$, and one was inactive ($\text{IC}_{50} > 12.5$ $\mu\text{g/ml}$) in comparison to chloroquine (IC_{50} 0.17 $\mu\text{g/ml}$), the positive control. Regarding *in vitro* antitrypanosomal activity, only one

compound showed promising activity with IC_{50} 1.85 $\mu\text{g/ml}$ (IC_{90} 3.4 $\mu\text{g/ml}$) using melarsoprol (IC_{50} 0.000011) as positive control.

The previous results represent the first report on the antitrypanosomal activity of pregnane glycosides, which encouraged the authors to test some of the previously isolated pregnane glycosides. The study carried by Abdel-Sattar et al. (2009) revealed that all the acylated glycosides showed variable activity, except for penicilloside B isolated from

C. penicillata that was inactive (Abdel-Sattar et al. 2001), while penicilloside E (3) isolated from *C. tuberculata* (Abdel-Sattar et al. 2008) was the most active (IC_{50} 1.01 $\mu\text{g/ml}$). However, all the tested non-acylated glycosides (russeliosides B–D) including russelioside B were completely inactive. The authors suggested the urgent need to test the previously acylated pregnane glycosides, in addition to their alycones.



Gastroprotective and Antiulcer Activity

Gastric ulcer is an acid-induced injury of the lining mucosa of the digestive tract. It results in a serious health problem, which could lead to the high morbidity and mortality rates due to perforation, bleeding, and obstruction (Lanas and Chan 2017). The estimated prevalence of peptic ulcer disease globally is 5–10%, but recently, it showed a decrease in the incidence of new cases, and mortality associated with peptic ulcer (Lanas et al. 2011).

Three species of genus *Caralluma* including *C. edulis*, *C. tuberculata*, and *C. umbellata* are traditionally used for the treatment of gastric ulcers (Adnan et al. 2014). Several species showed antigastric effect, cytoprotective or ulcer heal activity, like *C. arabica* (Zakaria et al. 2002), *C. adscendens* var. *fimbriata* (Dakshayani et al. 2014), *C. flava* N.E.Br. (Al-Naqeb 2017; Raees 2018), *C. tuberculata* (Alharbi et al. 1994), *C. attenuata* (Garg et al. 2016), *C. quadrangula* (Ibrahim et al. 2016) and *C. penicillata* (Deflers) N.E.Br. (Albaser et al. 2014).

The traditional uses of several *Caralluma* species in the treatment of gastric ulcer, in addition to the biological studies which confirmed these uses, encouraged El-Shiekh and coauthors (2021c) to evaluate the possible gastroprotective effect of russelioside B in rat model of gastric ulcer. The study aimed to evaluate the possible protective effect of russelioside B in ethanol-induced gastric mucosal injury of rat model (El-Shiekh et al. 2021c). Russelioside B (50 mg/kg) as well as antodine (20 mg/kg) as positive standard were given by oral

gavage 1 h before ulcer induction using absolute ethanol (5 ml/kg). Pretreatment with russelioside B attenuated the gastric mucosal ulceration as proved by a decrease of ulcer index, and histological scores. The significant decrease of cytokine levels (TNF- α and IL-6 levels) and lowering myeloperoxidase activity proved its inhibition of gastric inflammation. In addition, the administration of russelioside B suppressed the gastric oxidative stress through inhibition of lipid peroxides by maintaining reduced glutathione and by lowering malondialdehyde. It was able also to ameliorate the sharp decline in the levels of vascular endothelial growth factor, heat shock protein-70, prostaglandin E2, and carbonic anhydrase inhibition activity induced by ethanol.

Gastroprotective Mechanism of Action

The potential of ulcer healing action of russelioside B (1) was mainly exerted through multi-mechanistic actions: cytoprotective, antiulcerogenic effects, suppression of gastric oxidative stress, and anti-inflammatory properties. It acts also through anti-apoptotic activities and enhanced gastric mucosal protection by upregulation of endothelial growth factor, normalization of heat shock protein-70, and prostaglandin E2. These actions were comparable in part to classical antiulcer drugs such as antodine. Therefore, russelioside B could be a powerful candidate for the treatment of gastric ulcer and as potent

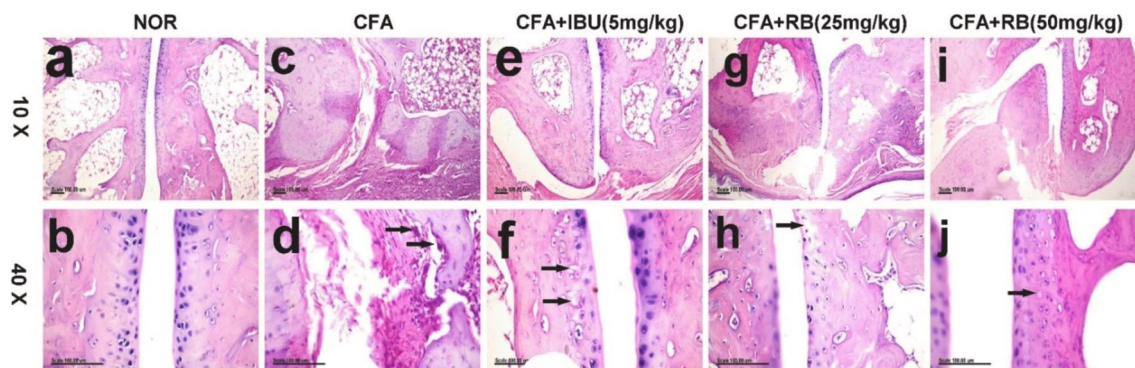


Fig. 2 Photomicrograph (hematoxylin and eosin staining, scale bar, 100 μm) of ankle joint of **a** and **b** normal group, **c** and **d** CFA group, **e** and **f** CFA + Ibuprofen group, **g** and **h** CFA + russelioside B group (25 mg/kg b. wt.), **i** and **j** CFA + russelioside B group (50 mg/kg b. wt.) (*n* = 8 rats per group). **a** Normal articular cartilage with smooth surface. **b** Normal chondrocytes embedded within normal cartilage matrix. **c** Deterioration of cartilage and subchondral bone. **d** numerous osteoclasts (arrows). **e**

Smooth articular surface. **f** Necrosis of chondrocytes (arrows). **g** Smooth articular surface. **h** Focal loss of cartilaginous matrix (arrow). **i** Normal cartilage matrix. **j** Necrosis of individual chondrocytes (arrow). Abbreviation: CFA, complete Freund’s adjuvant-induced arthritic rats; IBU, ibuprofen treated group; NOR, normal group; RB, russelioside B (1)–treated groups. Reproduced from El-Shiekh et al. (2021a)

Methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Acinetobacter baumannii* (MDRAB) are serious public health threat. It becomes a big challenge because of their capability to cause biofilm resistance to commonly used antibiotics producing chronic infections and hindering the process of wound healing. The antibacterial activity of *C. quadrangula* extracts (MeOH, and its fractions CH₂Cl₂ and *n*-butanol) was investigated against

multidrug-resistant MRSA USA300 and MDRAB AB5057 (El-Shiekh et al. 2021b). *In vitro*, all the tested samples of *C. quadrangula* significantly suppressed biofilm formation and destroyed the established biofilm of MRSA and MDRAB at all concentrations tested (0.625, 0.313, and 0.156 mg/ml). In addition, both *C. quadrangula* MeOH extract and the CH₂Cl₂-soluble fraction succeeded in lowering bacterial loads in MRSA-infected skin lesions in mice topically treated

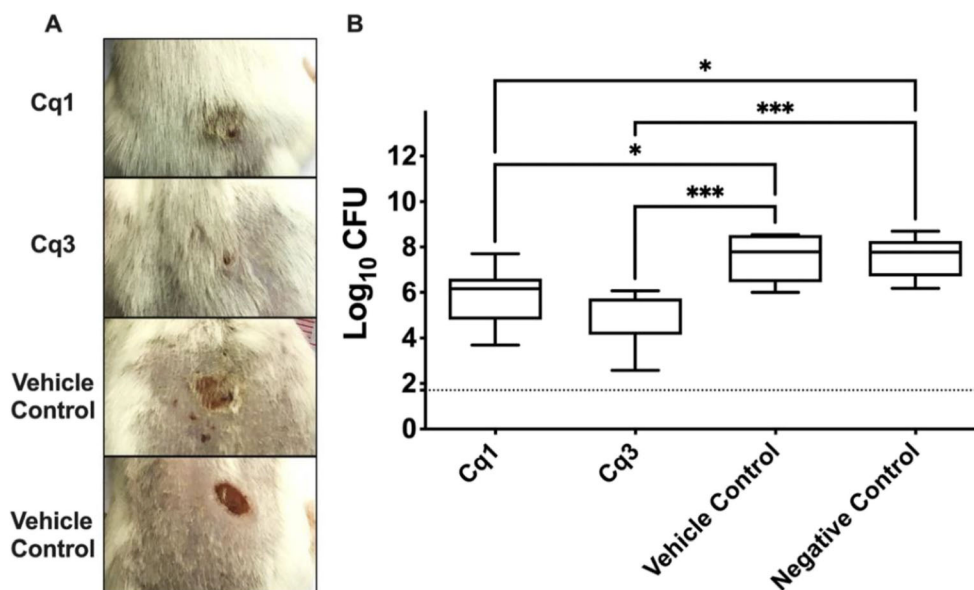
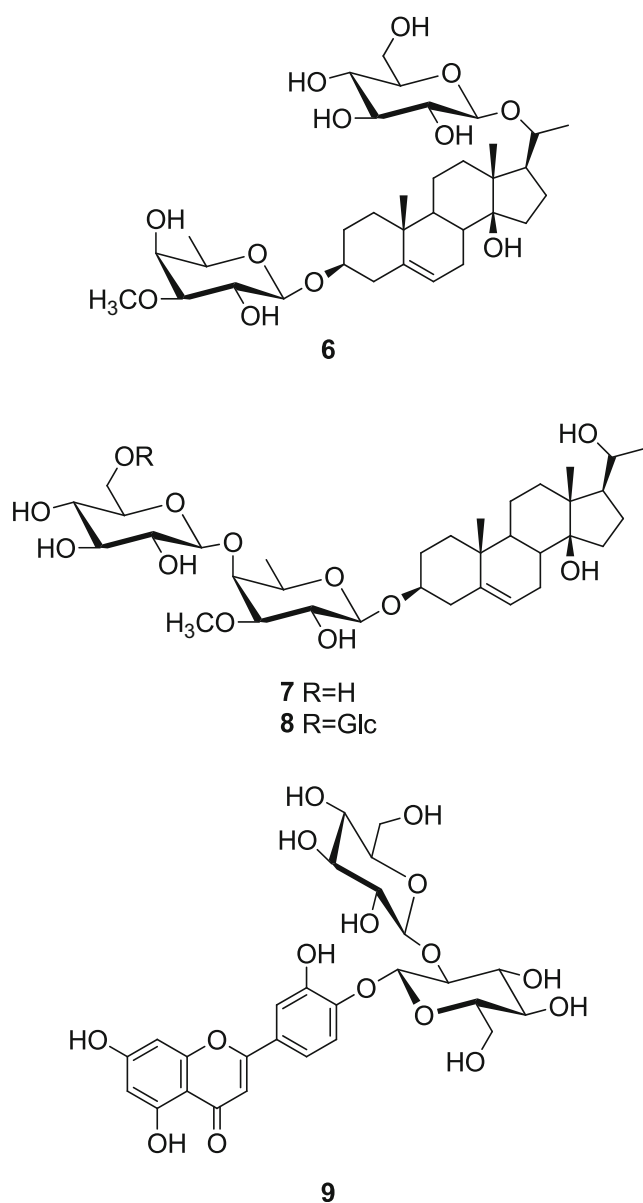


Fig. 3 Efficacy of *Caralluma quadrangula* MeOH extract (Cq1) and *n*-butanol fraction (Cq3) in a murine model of MRSA skin infection *in vivo*. Thirty-two BALB/C mice were divided into four groups (*n* = 8), three treated groups (Cq1, Cq3, and vehicle), and the fourth group remained untreated as the negative control. **A** Efficacy of *C. quadrangula* extracts (Cq1 and Cq3) on MRSA skin infection in the posterior upper backs of mice at the end of the experiment. **B** Efficacy of *C. quadrangula* extracts

on the bacterial load in murine model MRSA skin infection. Results are expressed as mean ± standard error. The dotted line represents the limit of detection of the viable count (log₁₀ of 50 CFU = 1.7). * and *** indicate that the difference is significant at *p* < 0.05 and *p* < 0.0009, respectively (one-way ANOVA, Tukey’s *post hoc* test). Reproduced from El-Shiekh et al. (2021b)



(Fig. 3). The chromatographic separation of the bioactive *n*-butanol led to the isolation of four pregnane glycosides (1, 6–8) and one flavone glycoside (9). All the isolated compounds, coded as Rus A–E (1, 6–9) were subjected to biofilm inhibition and biofilm detachment assays. Rus C (8) was the most active compound (IC_{50} 0.139 mmole), while Rus E (9) was the least active (IC_{50} 0.818 mmole). These results support the potential use of *C. quadrangula* extracts or their isolated compounds for inhibiting the biofilm attachment and the virulence of MRSA and MDRA B and their application as a topical antimicrobial preparation in MRSA skin infections.

Perspectives and Future Directions

Russelioside B (1) is considered a good lead for the development of a new phytopharmaceutical for the treatment of different ailments. In the previous studies, there is a lack for an ideal method for the isolation of russelioside B that generates a higher yield, in a shorter time and at a lower cost other than solvent-solvent extraction using *n*-butanol. In addition, russelioside B was determined only by LC-ESI for its quantification. Analytically, there is a need for simple methods for its metabolites, specifically in biological fluids. Compound 1 has shown different biological activities, such as antidiabetic, antibacterial, antiparasitic, anti-obesity, and gastroprotective potentials, but further detailed safety and pharmacokinetic studies are necessary. To date, there are no trials for the synthesis of 1; therefore, it is also necessary to prepare its derivatives and investigate their activity and construct structure-activity relationships and understand their mechanisms of action. Based on its activity on inflammatory biomarkers, compound 1 needs to be tested against COVID-19 infection.

Conclusions

This review presents updated report on russelioside B (1), a major pregnane glycosides isolated from different *Caralluma* species with a promising pharmacological preclinical potential. Russelioside B possesses anti-inflammatory, anti-obesity, antidiabetic, antibacterial, antigastric ulcer, and antibiofilm properties, as well as it could be useful for the treatment of rheumatic arthritis. The main limitation for its therapeutic use is the lack of detailed assessment of its safety profile on different organs, which are also required for a better evaluation of its potential for future clinical applications. Further deeper mechanistic studies underlying these beneficial properties are needed in a near future to elucidate the interaction between russelioside B and the receptors of the specific genes. This review suggests that russelioside B may find direct medicinal application as a phytopharmaceutical agent or as chemical template for the design, synthesis, and semi-synthesis of new drug for the treatment of contemporary human diseases.

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Author Contribution Both authors contributed equally, and have read and approved the final submission.

Declarations

Conflict of Interest The authors declare no competing interests.

References

- Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, Adams RJ, Aekplakom W, Afsana K, Aguilar-Salinas CA, Agyemang C (2017) Worldwide trends in body-mass index, overweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 390:2627–2642. [https://doi.org/10.1016/S0140-6736\(17\)32129-3](https://doi.org/10.1016/S0140-6736(17)32129-3)
- Abdel-Sattar E, Al-Yahya MA-A, Nakamura N, Hattori M (2001) Penicillosides A–C, C-15 oxypregnane glycosides from *Caralluma penicillata*. *Phytochemistry* 57:1213–1217. [https://doi.org/10.1016/S0031-9422\(01\)00163-7](https://doi.org/10.1016/S0031-9422(01)00163-7)
- Abdel-Sattar E, Harraz FM, Al-Ansari SM, El-Mekkawy S, Ichino C, Kiyohara H, Ishiyama A, Otaguro K, Omura S, Yamada H (2008) Acylated pregnane glycosides from *Caralluma tuberculata* and their antiparasitic activity. *Phytochemistry* 69:2180–2186. <https://doi.org/10.1016/j.phytochem.2008.05.017>
- Abdel-Sattar E, Shehab NG, Ichino C, Kiyohara H, Ishiyama A, Otaguro K, Omura S, Yamada H (2009) Antitrypanosomal activity of some pregnane glycosides isolated from *Caralluma* species. *Phytomedicine* 16:659–664. <https://doi.org/10.1016/j.phymed.2009.02.009>
- Abdel-Sattar E, Harraz FM, Ghareib SA, Elberry AA, Gabr S, Suliaman MI (2011) Antihyperglycaemic and hypolipidaemic effects of the methanolic extract of *Caralluma tuberculata* in streptozotocin-induced diabetic rats. *Nat Prod Res* 25:1171–1179. <https://doi.org/10.1080/14786419.2010.490782>
- Abdel-Sattar EA, Abdallah HM, Khedr A, Abdel-Naim AB, Shehata IA (2013) Antihyperglycemic activity of *Caralluma tuberculata* in streptozotocin-induced diabetic rats. *Food Chem Toxicol* 59:111–117. <https://doi.org/10.1016/j.fct.2013.05.060>
- Abdel-Sattar E, El-Maraghy SA, El-Dine RS, Rizk SM (2016) Russelloside B, a pregnane glycoside ameliorates hyperglycemia in streptozotocin induced diabetic rats by regulating key enzymes of glucose metabolism. *Chem-Biol Interact* 252:47–53. <https://doi.org/10.1016/j.cbi.2016.03.033>
- Abdel-Sattar E, SA EL-M, El-Dine RS, Rizk SM (2017) Antihyperglycemic activity of *Caralluma quadrangula* in streptozotocin-induced diabetic rats. *Bulletin of Faculty of Pharmacy, Cairo University* 55:269–272. <https://doi.org/10.1016/j.bfopcu.2017.07.002>
- Abdel-Sattar E, Mehanna ET, El-Ghaiesh SH, Mohammad HM, Elgendy HA, Zaitone SA (2018) Pharmacological action of a pregnane glycoside, russelloside B, in dietary obese rats: impact on weight gain and energy expenditure. *Front Pharmacol* 9:990. <https://doi.org/10.3389/fphar.2018.00990>
- Abdul-Aziz Al-Yahya M, Abdel-Sattar E, Guittet E (2000) Pregnane glycosides from *Caralluma russeliana*. *J Nat Prod* 63:1451–1453. <https://doi.org/10.1021/np990530c>
- Adnan M, Jan S, Mussarat S, Tariq A, Begum S, Afroz A, Shinwari ZK (2014) A review on ethnobotany, phytochemistry and pharmacology of plant genus *Caralluma* R. Br. *J Pharm Pharmacol* 66:1351–1368. <https://doi.org/10.1111/jphpp.12265>
- Ahmed MM, Qureshi S, Al-Bekairi AM, Shak AH (1993) Anti-inflammatory activity of *Caralluma tuberculata* alcoholic extract. *Fitoterapia* 64:357–357
- Al-Adhrai AM, Moqbel FS, Alqadasi A, Abd Algalil FM (2018) Antihyperglycemic activity of *Caralluma quadrangula* in alloxan-induced diabetic rats. *Int J Biol* 3:25–31
- Albaser N, Ghanem N, Shehab M, Al-Adhal A, Amood AL-Kamarany M (2014) Investigation of pharmacological activity of *Caralluma penicillata*: anti-inflammatory properties and gastritis protection against indomethacin in adult guinea pigs. *Int Scholar Res Notices* 2014:738493. <https://doi.org/10.1155/2014/738493>
- Alharbi MM, Qureshi S, Raza M, Ahmed MM, Afzal M, Shah AH (1994) Evaluation of *Caralluma tuberculata* pretreatment for the protection of rat gastric mucosa against toxic damage. *Toxicol Appl Pharm* 128:1–8. <https://doi.org/10.1006/taap.1994.1173>
- Al-Naqeb G (2017) Acute toxicity and anti-ulcerative potential of *Caralluma flava* NE Br methanolic extract against ethanol-induced gastric ulcers in rats. *J Med Plants* 5:21–25
- Ambadasu B, DSWRW PS (2013) Effect of *Caralluma fimbriata* extract on appetite and lipid profile in rats fed with hypercalorie/cafeteria diet. *Int J Pharm and Bio Sci* 4:788–793
- Arvigo R, Balick MJ (1993) Rainforest remedies: one hundred healing herbs of Belize. Lotus Press
- Ashley EA, Phyo AP, Woodrow CJ (2018) Malaria. *Lancet* 391:1608–1621. [https://doi.org/10.1016/S0140-6736\(18\)30324-6](https://doi.org/10.1016/S0140-6736(18)30324-6)
- Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT (2021) Natural products in drug discovery: advances and opportunities. *Nat Rev Drug Discov* 20:200–216. <https://doi.org/10.1038/s41573-020-00114-z>
- Atlas D (2015) International Diabetes Federation. IDF Diabetes Atlas, 7th edn. International Diabetes Federation, Brussels, Belgium
- Babu KS, Malladi S, Nadh RV, Rambabu SS (2014) Evaluation of *in vitro* antibacterial activity of *Caralluma umbellata* Haw used in traditional medicine by Indian tribes. *Ann Res Rev Biol*:840–855. <https://doi.org/10.9734/ARRB/2014/6401>
- Balandrin MF, Kinghorn AD, Farnsworth NR (1993) Plant-derived natural products in drug discovery and development: an overview. <https://doi.org/10.1021/bk-1993-0534.ch001>
- Balunas MJ, Kinghorn AD (2005) Drug discovery from medicinal plants. *Life Sci* 78:431–441. <https://doi.org/10.1016/j.lfs.2005.09.012>
- Beutler JA (2009) Natural products as a foundation for drug discovery. *Curr Protoc Pharmacol* 46:9–11. <https://doi.org/10.1002/0471141755.ph0911s46>
- BinMowyna MN, Alsayadi MM (2020) Assessment of the antioxidant and antimicrobial activities of *Caralluma deflersiana* growing in the South of Saudi Arabia. *Afr J Pharm Pharmacol* 14:331–338. <https://doi.org/10.5897/AJPP2020.5183>
- Braca A, Bader A, Morelli I, Scarpato R, Turchi G, Pizza C, De Tommasi N (2002) New pregnane glycosides from *Caralluma negevensis*. *Tetrahedron* 58:5837–5848. [https://doi.org/10.1016/S0040-4020\(02\)00563-X](https://doi.org/10.1016/S0040-4020(02)00563-X)
- Butler MS (2008) Natural products to drugs: natural product-derived compounds in clinical trials. *Nat Prod Rep* 25:475–516. <https://doi.org/10.1039/B402985M>
- Cho N, Shaw J, Karuranga S, Yd H, da Rocha FJ, Ohlrogge A, Malanda B (2018) IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pr* 138:271–281. <https://doi.org/10.1016/j.diabres.2018.02.023>
- Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, Williams B, Gabriel S, Lassere M, Johns N, Buchbinder (2014) The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 73:1316–1322. <https://doi.org/10.1136/annrheumdis-2013-204627>
- Dakshayani MM, Vidyasagar G, Nithin Kamalakar Rao M, Prasad K (2014) Anti-ulcerogenic activity of *Caralluma adscendens* var. *fimbriata* aerial part extracts against experimentally-induced gastric lesions in rats. *Int J Pharm Bio Sci* 4:788–793
- El-Shiekh RA, El-Mekkawy S, Mounair SM, Hassan A, Abdel-Sattar E (2021a) Therapeutic potential of russelloside B as anti-arthritis agent in Freund's adjuvant-induced arthritis in rats. *J Ethnopharmacol* 270:113779. <https://doi.org/10.1016/j.jep.2021.113779>
- El-Shiekh RA, Hassan M, Hashem RA, Abdel-Sattar E (2021b) Bioguided isolation of antibiofilm and antibacterial pregnane glycosides from *Caralluma quadrangula*: disarming multidrug-resistant pathogens. *Antibiotics* 10:811. <https://doi.org/10.3390/antibiotics10070811>

- El-Shiekh RA, Salama A, Al-Mokaddem AK, Bader A, Abdel-Sattar EA (2021c) Russelioside B; a pregnane glycoside for treatment of gastric ulcer via modulation of heat shock protein-70 and vascular endothelial growth factor. *Steroids* 165:108759. <https://doi.org/10.1016/j.steroids.2020.108759>
- Farnsworth NR, Akerele O, Bingel AS, Soejarto DD, Guo Z (1985) Medicinal plants in therapy B *World Health Organ* 63:965–981 <https://apps.who.int/iris/handle/10665/265180>
- Farouk A, Ahamed NT, AlZahrani O, Alamer KH, Al-Sodany Y, Bahobail A (2016) Antimicrobial activity of *Caralluma quadrangula* (Forssk) NE Br latex from Al-ShafaTaif, Kingdom of Saudi Arabia. *Int J Curr Microbiol Appl Sci* 5:284–298. <https://doi.org/10.20546/ijcmas.2016.511.031>
- Garg S, Srivastava S, Singh K, Sharma A, Garg K (2016) Ulcer healing potential of ethanolic extract of *Caralluma attenuata* on experimental diabetic rats. *Ancient Sci Life* 35:222–226. <https://doi.org/10.4103/0257-7941.188182>
- Gonzalez-Hurtado E, Lee J, Choi J, Wolfgang MJ (2018) Fatty acid oxidation is required for active and quiescent brown adipose tissue maintenance and thermogenic programming. *Mol Metab* 7:45–56. <https://doi.org/10.1016/j.molmet.2017.11.004>
- Gummadi SB, Belvotagi VAR, Kommidi DR, Bobbala RK, Achanta VAR, Sterner O (2021) Steroidal glycosides from *Caralluma pauciflora*. *Phytochem Lett* 41:43–48. <https://doi.org/10.1016/j.phytol.2020.10.016>
- Gurib-Fakim A (2006) Medicinal plants: traditions of yesterday and drugs of tomorrow. *Mol Aspects Med* 27:1–93. <https://doi.org/10.1016/j.mam.2005.07.008>
- Habibuddin M, Daghriri HA, Humaira T, Al Qahtani MS, Hefzi AAH (2008) Antidiabetic effect of alcoholic extract of *Caralluma sinaica* L. on streptozotocin-induced diabetic rabbits. *J Ethnopharmacol* 117:215–220. <https://doi.org/10.1016/j.jep.2008.01.021>
- Han S-F, Jiao J, Zhang W, Xu J-Y, Zhang W, Fu C-L, Qin L-Q (2017) Lipolysis and thermogenesis in adipose tissues as new potential mechanisms for metabolic benefits of dietary fiber. *Nutrition* 33:118–124. <https://doi.org/10.1016/j.nut.2016.05.006>
- Hanl K, Kimura Y, Okuda H (2005) Anti-obesity effects of natural products. In: *Studies in natural products chemistry*, vol 30. Elsevier, pp 79–110. [https://doi.org/10.1016/S1572-5995\(05\)80031-6](https://doi.org/10.1016/S1572-5995(05)80031-6)
- Harvey AL (2008) Natural products in drug discovery. *Drug Discov Today* 13:894–901. <https://doi.org/10.1016/j.drudis.2008.07.004>
- Ibrahim IA, Abdulla MA, Hajrezaie M, Bader A, Shahzad N, Al-Ghamdi SS, Gushash AS, Hasanpourghadi M (2016) The gastroprotective effects of hydroalcoholic extract of *Monolluma quadrangula* against ethanol-induced gastric mucosal injuries in Sprague Dawley rats. *Drug Des Dev Ther* 10:93–105. <https://doi.org/10.2147/DDDT.S91247>
- Kassebaum NJ, Arora M, Barber RM, Bhutta ZA, Brown J, Carter A, Casey DC, Charlson FJ, Coates MM, Coggeshall M, Cornaby L (2016) Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 388:1603–1658. [https://doi.org/10.1016/S0140-6736\(16\)31460-X](https://doi.org/10.1016/S0140-6736(16)31460-X)
- Kayser O, Kiderlen A, Croft S (2003) Natural products as antiparasitic drugs. *Parasitol Res* 90:S55–S62. <https://doi.org/10.1007/s00436-002-0768-3>
- Kumar VH (2016) Anti-hyperglycemic effect of *Caralluma lasiantha* extract on hyperglycemia induced by cafeteria-diet in experimental model. *Int J Pharm Sci Res* 7:2525–S504. https://doi.org/10.4103/pm.pm_59_17
- Kumar KP, Khan KA, Anupama K, Prakash KV (2008) Antifungal and antihelmintic activity of *Caralluma fimbriata* stem: a herb. *Int J Chem Sci* 6:1486–1490
- Lanas A, Chan FK (2017) Peptic ulcer disease. *Lancet* 390:613–624. [https://doi.org/10.1016/S0140-6736\(16\)32404-7](https://doi.org/10.1016/S0140-6736(16)32404-7)
- Lanas A, García-Rodríguez LA, Polo-Tomás M, Ponce M, Quintero E, Perez-Aisa MA, Gisbert JP, Bujanda L, Castro M, Muñoz M, Del-Pino MD (2011) The changing face of hospitalisation due to gastrointestinal bleeding and perforation. *Aliment Pharm Ther* 33:585–591. <https://doi.org/10.1111/j.1365-2036.2010.04563.x>
- Latha S, Rajaram K, Suresh Kumar P (2014) Hepatoprotective and anti-diabetic effect of methanol extract of *Caralluma fimbriata* in streptozotocin induced diabetic albino rats. *Int J Pharm Pharm Sci* 6:665–668
- Liu S, Chen Z, Wu J, Wang L, Wang H, Zhao W (2013) Appetite suppressing pregnane glycosides from the roots of *Cynanchum auriculatum*. *Phytochemistry* 93:144–153. <https://doi.org/10.1016/j.phytochem.2013.03.010>
- Lwin MN, Serhal L, Holroyd C, Edwards CJ (2020) Rheumatoid arthritis: the impact of mental health on disease: a narrative review. *Rheumatol Ther* 7:457–471. <https://doi.org/10.1007/s40744-020-00217-4>
- Makeen HA, Menachery SJ, Moni SS, Alqahtani SS, ur Rehman Z, Alam MS, Mohan S, Albratty M (2020) Documentation of bioactive principles of the exudate gel (EG) from the stem of *Caralluma retropiciens* (Ehrenb) and *in vitro* antibacterial activity—Part A. *Arab J Chem* 13:6672–6681. <https://doi.org/10.1016/j.arabjc.2020.06.022>
- Malladi S, Ratnakaram VN, Suresh Babu K, Pullaiah T (2017) Evaluation of *in vitro* antibacterial activity of *Caralluma lasiantha* for scientific validation of Indian traditional medicine. *Cogent Chem* 3:1374821. <https://doi.org/10.1080/23312009.2017.137482>
- Morinaga H, Yamamoto H, Sakata K, Fukuda S, Ito M, Sasase T, Miyajima K, Ueda N, Ohta T, Matsushita M (2008) Characterization of hepatic glucose metabolism disorder with the progress of diabetes in male spontaneously diabetic torii rats. *J Vet Med Sci* 70:1239–1245. <https://doi.org/10.1292/jvms.70.1239>
- Naik J, Jadge D (2009) Antiinflammatory activity of ethanolic and aqueous extracts of *Caralluma adscendens*. *J Pharm Res* 2:1228–1229
- Naingade S, Jadhav A, Surve S (2013) *Caralluma fimbriata*: an overview. *Int J Pharm Bio Sci* 3:281–286
- Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. *J Nat Prod* 70:461–477. <https://doi.org/10.1021/np068054v>
- Newman DJ, Cragg GM (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J Nat Prod* 75:311–335. <https://doi.org/10.1021/np200906s>
- Newman DJ, Cragg GM (2016) Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* 79:629–661. <https://doi.org/10.1021/acs.jnatprod.5b01055>
- Newman DJ, Cragg GM (2020) Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod* 83:770–803. <https://doi.org/10.1021/acs.jnatprod.9b01285>
- Newman DJ, Cragg GM, Snader KM (2000) The influence of natural products upon drug discovery. *Nat Prod Rep* 17:215–234. <https://doi.org/10.1039/a902202c>
- Newman DJ, Cragg GM, Snader KM (2003) Natural products as sources of new drugs over the period 1981–2002. *J Nat Prod* 66:1022–1037. <https://doi.org/10.1021/np030096l>
- Radhakrishnan R, Zakaria M, Islam M, Liu X, Chan K, Habibullah M (1999) Antihyperglycaemic effects of *Caralluma arabica* in diabetic mice. *J Pharm Pharmacol* 51:116–116. <https://doi.org/10.1080/14786419.2010.490782>
- Raees MA (2018) A phytopharmacological review on an Arabian medicinal plant: *Caralluma flava* NE Br. *Int. J. Phytomed* 10:148–152. <https://doi.org/10.5138/09750185.2257>
- Ramanjaneyulu C, Viswanath Y, Ramakrishna C, Kumar PA, Kalyani V, Chakrapani B (2016) Evaluation of anti-inflammatory activity of petroleum spirit extract of *Caralluma umbellata*. *International Journal of Trends in Pharmacy and Life Sciences* 2:895–906

- Ramesh M, Rao YN, Rao AA, Prabhakar M, Rao CS, Muralidhar N, Reddy BM (1998) Antinociceptive and anti-inflammatory activity of a flavonoid isolated from *Caralluma attenuata*. *J Ethnopharmacol* 62:63–66. [https://doi.org/10.1016/s0378-8741\(98\)00048-8](https://doi.org/10.1016/s0378-8741(98)00048-8)
- Rameshreddy P, Uddandrao VV, Brahmanaidu P, Vadivukkarasi S, Ravindarnaik R, Suresh P, Swapna K, Kalaivani A, Parvathi P, Tamilmani P, Saravanan G (2018) Obesity-alleviating potential of asiatic acid and its effects on ACC1, UCP2, and CPT1 mRNA expression in high fat diet-induced obese Sprague–Dawley rats. *Mol Cell Biochem* 442:143–154. <https://doi.org/10.1007/s11010-017-3>
- Ray S, Nagaiah K, Khan NF (2011) Anti-inflammatory activity of carumbelloside-III, isolated from *Caralluma umbellata*. *NSHM J Pharm Health Mgt* 2:83–88. [https://doi.org/10.1016/s0378-8741\(99\)00122-1](https://doi.org/10.1016/s0378-8741(99)00122-1)
- Ray S, Nagaiah K, Khan NF (2012) A study of anti-inflammatory activity of one novel C-21 steroidal glycoside known as carumbelloside-IV isolated from *Caralluma umbellata*. *J PharmaSciTech* 1:12–14
- Reddy KD, Reddy KH, Rao GV, Brenda M, Patrick G, Koorbanally NA (2011) Minor pregnanes from *Caralluma adscendens* var. *gracilis* and *Caralluma pauciflora*. *Fitoterapia* 82:1039–1043. <https://doi.org/10.1016/j.fitote.2011.06.011>
- Reddy KD, Reddy KH, Rao GV, Brenda M, Patrick G, Koorbanally NA (2013) *In vitro* antimicrobial, antioxidant and cytotoxic activities of new pregnane glycosides and pregnanes isolated from the *Caralluma adscendens* var. *gracilis* and *Caralluma pauciflora*. *J Pure Appl Microbiol* 7:2707–2712
- Sayantana R, Abhishek S (2012) Antidiabetic activity of *Caralluma edulis* bark and leaf extract against streptozotocin induced diabetic rats. *NSHM J Pharm Healthcare Management* 3:76–81
- Schrauwen P, Westerterp KR (2000) The role of high-fat diets and physical activity in the regulation of body weight. *Br J Nutr* 84:417–427. <https://doi.org/10.1017/S0007114500001720>
- Sethi A, Maurya A, Tewari V, Srivastava S, Faridi S, Bhatia G, Khan MM, Khanna AK, Saxena JK (2007) Expedient and convenient synthesis of pregnanes and its glycosides as potential anti-dyslipidemic and anti-oxidant agents. *Bioorgan Med Chem* 15:4520–4527. <https://doi.org/10.1016/j.bmc.2007.04.022>
- Shao C, Bai L-P, Qi Z-Y, Hui G-Z, Wang Z (2014) Overweight, obesity and meningioma risk: a meta-analysis. *PloS One* 9:e90167. <https://doi.org/10.1371/journal.pone.0090167>
- Shashoua VE, Hesse GW (1996) *N*-docosahexaenoyl,3-hydroxytyramine: a dopaminergic compound that penetrates the blood-brain barrier and suppresses appetite. *Life Sci* 58:1347–1357. [https://doi.org/10.1016/0024-3205\(96\)00101-4](https://doi.org/10.1016/0024-3205(96)00101-4)
- Shuaib M, Kushwaha PP, Prajapati KS, Singh AK, Sharma R, Kumar S (2021) Effect of dietary phytochemicals in obesity and cancer. In: Kumar S, Gupta S (eds) *Obesity and cancer*. Springer, Singapore, pp 163–184. https://doi.org/10.1007/978-981-16-1846-8_9
- Singh V, Kori ML (2014) Antidiabetic effect of hydroalcoholic combined plant extract of *Portulaca oleracea* and *Caralluma attenuata* in streptozotocin induced diabetic rats. *Indo Amer J Pharm Res* 4:1391–1396
- Son JW, Kim S (2020) Comprehensive review of current and upcoming anti-obesity drugs. *Diabetes Metab J* 44:802–818. <https://doi.org/10.4093/dmj.2020.0258>
- Tanko Y, Halidu A, Mohammed A, Ahmed M, Musa K (2012) Effect of ethanol extract of *Caralluma dalzielii* NE Br.(Asclepiadaceae) on blood glucose levels of fructoseinduced insulin resistance in laboratory. *Ann Biol Res* 3:4980–4984
- Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, Dzobo K (2018) Natural products for drug discovery in the 21st century: innovations for novel drug discovery. *Int J Mol Sci* 19:1578. <https://doi.org/10.3390/ijms19061578>
- Tucci SA (2010) Phytochemicals in the control of human appetite and body weight. *Pharmaceuticals* 3:748–763. <https://doi.org/10.3390/ph3030748>
- Umar A, Mabrouk M, Danjuma N, Yaro A (2013) Studies on the analgesic and anti-inflammatory properties of hydro-alcohol extract of *Caralluma dalzielii* NE Br (Asclepiadaceae) in rats and mice. *Br J Pharmacol Toxicol* 4:169–175
- Venkatesh S, Reddy GD, Reddy BM, Ramesh M, Rao AA (2003) Antihyperglycemic activity of *Caralluma attenuata*. *Fitoterapia* 74:274–279. [https://doi.org/10.1016/s0367-326x\(03\)00021-2](https://doi.org/10.1016/s0367-326x(03)00021-2)
- Vermaak I, Hamman JH, Viljoen AM (2011) *Hoodia gordonii*: an up-to-date review of a commercially important anti-obesity plant. *Planta Med* 77:1149–1160. <https://doi.org/10.1055/s-0030-1250643>
- Wadood A, Wadood N, Shah S (1989) Effects of *Acacia arabica* and *Caralluma edulis* on blood glucose levels of normal and alloxan diabetic rabbits. *J Pak Med Assoc* 39:208–212
- WHO (2020) World malaria report 2020: 20 years of global progress and challenges. Global Malaria Programme, Geneva, 299 p
- Yoshikawa M (2002) Constituent for preventing diabetes. *Kagaku Seibutsu* 40:172–178
- Zaitone SA, Barakat BM, Bilasy SE, Fawzy MS, Abdelaziz EZ, Farag NE (2015) Protective effect of boswellic acids versus pioglitazone in a rat model of diet-induced non-alcoholic fatty liver disease: influence on insulin resistance and energy expenditure. *Naunyn-Schmiedeberg's Arch Pharmacol* 388:587–600. <https://doi.org/10.1007/s00210-015-1102-9>
- Zakaria M, Islam M, Radhakrishnan R, Chen H, Kamil M, Al-Gifri A, Chan K, Al-Attas A (2001) Anti-nociceptive and anti-inflammatory properties of *Caralluma arabica*. *J Ethnopharmacol* 76:155–158. [https://doi.org/10.1016/s0378-8741\(01\)00208-2](https://doi.org/10.1016/s0378-8741(01)00208-2)
- Zakaria M, Islam M, Radhakrishnan R, Liu X, Ismail A, Kamil M, Chan K, Al-Attas A (2002) Anti-gastric ulcer and cytoprotective properties of *Caralluma arabica*. *Pharm Biol* 40:225–230. <https://doi.org/10.1076/phbi.40.3.225.5830>
- Zari TA, Al-Thebaiti MA (2018) Effects of *Caralluma russeiliana* stem extract on some physiological parameters in streptozotocin-induced diabetic male rats. *Diabetes Metab Syndr* 2018:619–631. <https://doi.org/10.2147/DMSO.S167293>
- Zielinski MR, Systrom DM, Rose NR (2019) Fatigue, sleep, and autoimmune and related disorders. *Front Immunol* 10:1827. <https://doi.org/10.3389/fimmu.2019.01827>