# Chapter 38

# Therapeutic Potential of Sterculia Seeds in Metabolic Syndrome

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## ABSTRACT

Metabolic syndrome (MetS) represents a significant health concern globally, necessitating diverse strategies for its management. Non-pharmacological approaches, including lifestyle modifications, dietary adjustments, and the incorporation of nutraceutical and functional foods, play a crucial role in addressing MetS. Among the plant genera showing promise in alleviating MetS is *Sterculia*, a member of the Malvaceae family encompassing over 200 species with documented ethnopharmacological uses. The seeds composition of certain *Sterculia* species has been studied, revealing compounds with therapeutic potential. This chapter focuses on the promising effects of antioxidant compounds and cyclic fatty acids found in *Sterculia* seeds. These bioactive constituents hold the potential for preventing or treating the metabolic abnormalities of MetS.

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# INTRODUCTION

Metabolic syndrome (MetS) is currently one of the most important public health problems in the world. It is considered one of the most persistent epidemics globally, silently spreading with a high annual morbidity rate and a steady increase leading to the appearance of metabolic diseases early in life (Saklayen, 2018). The prevalence of MetS varies according to geographical region, place of residence, population composition, and the type of definition used. However, it is estimated globally to range from 10 to 84%, with an average of 20-25% in the adult population (Sherling et al., 2017).

MetS is characterized by the combination of three or more metabolic abnormalities that are interconnected and associated with a two-fold higher risk of developing cardiovascular diseases and a five times higher risk of developing type 2 diabetes mellitus, two of the principal metabolic diseases nowadays (Grundy et al., 2004; Aguilar-Salinas and Viveros-Ruiz, 2019). The main manifestations of MetS include insulin resistance, abdominal obesity, hypertension, atherogenic dyslipidemia (elevated blood levels of triglycerides and LDL-cholesterol, and low levels of HDL-cholesterol), high fasting serum glucose concentrations, endothelial dysfunction, oxidative stress, chronic low-grade inflammation and pro-thrombotic state (Kaur, 2014; Grundy, 2016; Harrison et al., 2020).

The pathogenesis of MetS may involve a genetic or epigenetic origin or can be the result of environmental and lifestyle factors, such as diet (quantity and quality), gut microbiota, or physical activity, considered as the main etiological factors. Among the mechanisms suggested explaining the pathophysiology of MetS, the most important is related to the presence of insulin resistance (IR), which is strongly interconnected with visceral obesity, inflammation, and oxidative stress. Adipose tissue plays a predominant role in the development of MetS. Besides functioning as an energy depot, it is a physiologically active tissue that secretes hormones like leptin and adiponectin, which control appetite and satiety, and regulate energy metabolism (Saklayen, 2018). Additionally, visceral fat promotes IR and the release of fatty acids that accumulate in organs such as the liver and muscle, further predisposing to IR, dyslipidemia, and oxidative stress. Adipose tissue also produces pro-inflammatory adipokines such as interleukins IL-1 $\beta$  and IL-6, and tumor necrosis factor-alpha (TNF- $\alpha$ ), generating a state of low-grade chronic inflammation in tissues (Zand et al., 2017; Mastrocola et al., 2018). Inflammation also affects vasodilation, causing arterial hypertension, leading to serious cardiovascular problems (Kaur, 2014). In recent years, various studies have

documented the important role of the increased activity of the enzyme stearoyl-CoA desaturase (SCD) in diseases such as cancer, Alzheimer's disease, skin disorders, and particularly in those associated with MetS. In consequence, it has become a new therapeutic target for the treatment of these pathologies (Peláez et al., 2020).

An effective strategy for managing MetS should include prevention, early diagnosis, and a multifactorial medical approach. Both pharmacological and non-pharmacological strategies have been applied, with combined treatments being the preferred option. Pharmacological treatments mainly focus on the individual components of the syndrome, with medications such as statins for treating dyslipidemia, or aspirin, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers for treating hypertension, as well as drugs to reduce insulin resistance, such as metformin and thiazolidinediones (Kuete, 2017).

On the other hand, non-pharmacological strategies have a greater impact than pharmacological ones, as they address the problem comprehensively. They involve lifestyle changes, such as dietary modifications for weight reduction and maintenance, and the inclusion of bioactive compounds and nutraceuticals, such as polyphenols, vitamins, omega-3 polyunsaturated fatty acids, with activities as antioxidants, vasodilators, anti-atherogenic, antithrombotic, and anti-inflammatory (De la Iglesia et al., 2016; Rochlani et al., 2017). Dietary antioxidants can exert preventive and/or therapeutic effects on some metabolic alterations. These compounds are found in foods, such as vegetables, legumes, fruits, and seeds, or might be administered in supplements. Their mechanisms of action is related to the maintenance or restoration of the redox homeostasis by its interaction with the endogenous antioxidant defense system (Durazzo et al., 2021). In addition to MetS, this homeostasis unbalance can be provoked by the overproduction of free radicals caused by pollution, ultraviolet radiation, smoking, and infections, which together may cause cancer, diabetes, cardiovascular and neurodegenerative diseases (Masenga et al., 2023).

Dietary lipids have received a lot of attention in dietary recommendations that usually include replacing dietary saturated fatty acids with unsaturated fats or with carbohydrates from whole grains foods. However, the diverse effects of specific fatty acids and the interindividual variability of responses make it challenging to establish specific recommendations (Harrison et al., 2020). In recent years, special interest has been given to cyclopropenoic fatty acids contained in the seeds' oil of plants from the genus *Sterculia*, due to their activity as inhibitors of the enzyme SCD (Peláez et al., 2020).

#### Sterculia Genus

The Malvaceae family comprises tropical flowering trees and shrubs, and some climbing and herbaceous species; contains over 240 genera and nearly 2300 species (Thabet et al., 2018). These plants possess secondary metabolites, including flavonoids and other compounds with diverse bioactivities. Flowers and seeds from *Hibiscus* and *Theobroma* have applications in the food industry, while fibers from *Gossypium*, such as cotton, are used in the textile industry (Robles-Valdivia and Sánchez-Otero, 2022). Among the key genera, *Sterculia* stands out for its commercial and medicinal significance (El-Sherei et al., 2016).

The genus *Sterculia* belongs to the subfamily Sterculioideae, and includes 200 species approximately, mainly distributed in tropical and subtropical regions (pantropical genus) (Rodríguez and Santamaría-Aguilar, 2020). Species within the *Sterculia* genus are notably prevalent in the Asian tropics, while in the Americas, approximately 38 species are reported (Fig. 1). These species thrive in diverse habitats, including tropical rainforests, humid and very humid forests, and altitudes of up to 1600 meters above sea level (Rodríguez and Santamaría-Aguilar, 2020).



**Fig. 1:** Distribution of *Sterculia* genus in the world. (Own elaboration in www.mapchart.net adapted from POWO, 2024. http://www.plantsoftheworldonline.org/).



**Fig. 2:** Trees, leaves, flowers, fruits, and seeds of *Sterculia* species. A) *S. urens*, B) *S. rogersii*, C) *S. africana*, D) *S. apetala*, E) *S. mexicana*, F) *S stigera*, G) *S. murex*, H) *S. quadrifida*, I) *S. gutata*, J) *S. africana*, K) *S. apetala*, L) *S. mexicana*, M) *S. lanceolata*. From https://mexico.inaturalist.org/observations (All images licensed CC-BY).

#### **General Description**

*Sterculia* species are bushes or trees, reaching heights of up to 45-50m. They feature large leaves, arranged alternately or spirally along the stems. Leaves can be simple and entire or exhibit 3 to 5 lobes or digitately compound structures. The inflorescences are typically axillary or terminal, forming panicles or occasionally racemes, and are multifloral, often adorned with trichomes. The flowers are actinomorphic, either staminate or possessing pistils. The fruits are generally pendulous and comprise up to 5 follicles. They are ovoid in shape, with surfaces that can be smooth or rough, usually brown, yellow, or green, which may turn red upon maturation and open upon ripening. The pericarp is woody, with villi on the outside and rigid trichomes, often urticant, on the inside. The seeds may range from 1 to 22 per follicle, depending on the species (Rodríguez and Santamaría-Aguilar, 2020) (Fig. 2).

*Sterculia* species have diverse applications in pharmacology and traditional medicine, as substitutes for tobacco in cigarettes or as flavoring agents in tobacco products, for paper manufacturing, for construction, and in biodiesel production (Bindhu et al., 2012; El-Sherei et al., 2016).

#### Seeds

The seeds are typically encased within a black hard shell. They are ovoidal or oblong in shape and commonly possess fleshy cotyledons and abundant endosperm (Fig. 3). They are consumed by people raw, boiled, or roasted and also serve as animal forage (De Britto Policarpi et al., 2018; Rodríguez and Santamaría-Aguilar, 2020).



**Fig. 3:** Seeds of different species of *Sterculia*. A) *S. cordata, B) S. foetida, C) S. africana, D) S. monosperma, E) S. quadrifida, F) S. apetala.* From: https://mexico.inaturalist.org/ observations (All images licensed CC-BY).

#### Phytochemistry and Bioactivities Associated with Sterculia Seeds

Seeds from *Sterculia* are composed of various proportions of lipids, proteins, carbohydrates, water, fiber, and ashes. For instance, *S. foetida* seeds are rich in lipids, constituting up to 52% of their cotyledons, with 21% protein, 22% carbohydrates, and 4% ashes (Ong et al., 2013). Phytochemical studies have identified a diverse array of compounds within *Sterculia* seeds, including fatty acids, saponins, alkaloids, phenylpropanoids, flavonoids, tannins, and terpenoids (Table 1) (De Britto Policarpi et al., 2018; Jafri et al., 2019).

**Table 1:** Compounds present in seeds from Sterculia species.

Table 1. Compounds present in seeds nom sta		
	specie	
(Flavonols)	s. iychnophora	vvang et al., 2003
Kaempterol-3-O-b-D-glucoside		
Isorhamnentin-3-O-b-D-rutinoside		
(Phytosterols)		
b-sitosterol		
(Alkaloids)		
Sterculinine I and II		
(Glycosphingolipids)		Wang et al., 2013
Cerebroside I and II		
Water-soluble polysaccharide fraction		Wu et al., 2008
(Phytosterols)	S. striata	De Britto Policarpi et al., 2018
β-Sitosterol		
Campesterol		
Stigmasterol		
(Tocopherols)		
α-Tocopherol		
β-Tocopherol		
γ-Tocopherol		
δ-Tocopherol		
(Phenolic compounds)		
Vainillic acid		
Ferulic acid		
Ellagic acid		
Catechin		
Rosmarinic acid		
(Alkaloids)	S. foetida	Jafri et al., 2019
Capsaicin		
(Phytosterols)		
g-Sitosterol		
(Esters)		
Butvl-citrate		
(Esssential aminoacids)	S. urens	Galla et al., 2012
Histidine		
Isoleucine		
Leucine		
Lysine		
Methionine		
Phenylalanine		
Threonine		
Valine		
(Esssential aminoacids)	S. murex	Regnier et al. 2017
Histidine		
Isoleucine		
Leucine		
Glutamic acid		
Cyclopropenoic fatty acids	S foetida	Rani et al. 2010
Sterculic acid	S. foetida	Ong et al. 2013
	S. foetida	Kavitha and Murugavelh 2019
	S foetida	Alam et al. 2021
	S. poetida	Herrora-Meza et al $201/$
	S. mexicana	Herrera-Meza et al. 2014
	S. mexicultu	Chaves et al. 2004
Cyclopropenaic fatty acids	S. su luitu S. anotala	Herrora-Meza et al. 2014
Cyclopiopenoic ratty actus Malvalic acid	s. upelulu S. movicana	Herrora Moza et al. 2012
	S. mexiculu S. footida	$\Box = \Box = \Box = 1000000000000000000000000000$
	S. juelluu	Uny et al., 2013 Kavitha and Murricaviale 2010
	S. juellaa	Kavitha and ividrugavein, 2019
Cuclic fatty acids	S. SITIULU	Cildves et al., 2004
	s. upelulu	nerrera ivieza et al., 2014
Dinydrosterculic acid	S. TAVIA	EI-Sherei et al., 2016

The ethnobotanical knowledge surrounding *Sterculia* plants is well-documented, particularly in Chinese and African traditional medicine. The leaves of *S. africana*, *S. striata*, and *S. setigera* are utilized to combat various microbial and fungal infections; the leaves of *S. foetida* are used as insect repellents and as laxative and diuretic; *S. setigera* bark is used for infertility treatments (Thabet et al., 2018); the seeds of *S. quadrifida* are utilized by Australian aboriginal communities to treat wounds, stings, and eye pain (Darojati et al., 2022); the leaves and bark of *S. apetala* are employed to alleviate respiratory illnesses, arthritis, and malaria (Rodríguez and Santamaría-Aguilar, 2020). The extracts and compounds of *Sterculia* species have also demonstrated antibacterial, insecticidal, cytotoxic, and antioxidant properties (Table 2).

Specie	Extract/Compound	Bioactivity	Reference
S. apetala	Hexanic/Sterculic oil	Cytotoxic	Contreras-López et al., 2022
		Prostate cancer treatment	
S striata	Aqueous	Antitumor	Alshambaty et al., 2021
S. villosa	Methanolic	Anxiolytic,sedative,	Barua et al., 2019
		cytotoxic	
S. foetida	Aqueous/Lectin	Antibacterial, hemolytic	Braga et al., 2015
S. foetida	Methanolic	Antimicrobial, antiosteosarcome	Jafri et al., 2019
S. foetida	Methanolic	Cytotoxic, thrombolytic, antiarthritic,	Alam et al., 2021
		analgesic, antipyretic	
S. guttata	Ethanolic	Anti-parkinsonism	Dhaliya-Salam et al., 2022
S. javanica	Extract (polarity not indicated)	Increase in spermatogenesis, sexual	Widianti et al., 2018
		behavior	
S. lychnophora	Polysaccharides	Probiotic bacteria proliferation	Huang et al., 2024
S. lychnophora	Ethanolic	Antibacterial	Yang et al., 2016
S. nobilis	Methanolic	Gastroprotective	Song et al., 2015

Table 2: Bioactivities nonrelated to MetS associated with seeds of Sterculia species.

Pharmacological studies focusing on *Sterculia* seeds metabolites applied to MetS and its manifestations are scarce. One of the most studied groups of compounds are the cyclic fatty acids (CFAs) present in their oil. CFAs are rare in nature, exhibit intriguing bioactivities, and constitute a significant percentage of the triacylglycerides found in *Sterculia* seeds (Dąbrowski and Konopka, 2022).

#### **Cyclopropenoic Fatty Acids**

The seeds of *Sterculia* species represent an interesting source of fats. These lipids commonly include the most prevalent fatty acids, such as palmitic, stearic, oleic, and linoleic acids, together with cyclic fatty acids (CFAs). CFAs are produced by certain bacteria, as well as plant species within the Malvales, Sapindales, and others, including *Litchi chinensis* (Dąbrowski and Konopka, 2022). Moreover, in some species of *Sterculia*, various fatty alcohols have been identified, such as docosanol, hexacosanol, and n-triacontanol (Thabet et al., 2018).

CFAs are characterized by the presence of a cyclopropane ring in their acyl chain. The CFA found in seeds of Malvaceous plant species is dihydrosterculic acid (cis-9,10-methylene octadecanoic acid). Additionally, cyclic acids containing a cyclopropene ring are referred to as cyclopropenoid fatty acids (CPFA). The two primary CPFA found in *Sterculia* seeds are sterculic acid (8-(2- octylcyclopropen-1-yl) octanoic acid) and malvalic acid (7-(2-octylcyclopropen-1-yl) heptanoic acid) (Dąbrowski and Konopka, 2022). Their structures are depicted in Fig. 4.



cyclopropenoid Fig. 4: Structures of fatty acids present in Sterculia seeds. A) Malvalic acid (https://www.wikidata.org/wiki/Q412814) acid (https://www.wikidata.org/wiki/Q2345401). B) Sterculic From: https://creativecommons.org/publicdomain/zero/1.0/ (Licensed CC-0).

Sterculic acid is recognized for its ability to inhibit the enzyme stearoyl-CoA desaturase (SCD) in both insects and animals; in insects, the inhibition of SCD can significantly impact maturation and reproduction, suggesting its potential as biocide agent<del>s</del> (Yu et al., 2011). In mammals, SCD plays a crucial role in lipid metabolism, making the inhibition of this enzyme a therapeutic target (Wang et al., 2015). Several investigations have analyzed the mechanisms underlying the effects of consuming sterculic oils as treatments for MetS and its manifestations.

#### **Cyclopropenoic Fatty Acids in Metabolic Syndrome**

Stearoyl-CoA desaturase (SCD) plays a key role in lipid metabolism since it catalyzes the synthesis of monounsaturated fatty acids, particularly oleic acid (18:1) and palmitic acid (16:1), which are the main fatty acids in adipose tissue (Gómez et al., 2003). Its inhibition has emerged as a promising therapeutic target since an increased SCD activity has been observed in animal models and humans with obesity, metabolic syndrome, diabetes, arteriosclerosis, cancer, Alzheimer's disease, skin disorders and viral infections (Ntambi et al., 2002; Warensjo et al., 2006; Hodson et al., 2013; Manni et al., 2017; Alsharari et al., 2017; Pelaez et al., 2020).

Genetic deletion or pharmacological inhibition of SCD has shown promising effects in improving various aspects of MetS in animal models. For example, transgenic mice lacking SCD do not develop obesity or insulin resistance when exposed to high-calorie diets. They exhibit lower body adiposity, enhanced insulin sensitivity in the liver, adipose tissue, and skeletal muscle, decreased hepatic triglycerides and cholesterol esters, elevated metabolic rates, and resistance to the development of non-alcoholic fatty liver disease (Rahman et al., 2005; Gutiérrez-Juárez et al., 2006; Miyazaki et al., 2009; Liu et al., 2010; Lounis et al., 2016). Recently, pharmaceutical companies have been developing synthetic SCD inhibitors as potential therapies for various liver diseases, dermatological conditions, Alzheimer's disease, and cancer (Uto, 2016).

Studies examining the impact of sterculic oil (SO) on metabolic syndrome have reported positive therapeutic effects (Table 3). Major et al. (2008) investigated the effects of SO supplementation in hamsters fed a high-fat and cholesterol diet, observing reductions in body weight and body adiposity. Ortinau et al. (2012) reported that SO administration in leptin-deficient *ob/ob* mice has beneficial effects on glucose tolerance, insulin resistance, and reduces liver inflammation. In another study, Ortinau et al. (2013) observed that the supplementation of obese OLETF rats with SO led to reductions in serum glucose concentrations, abdominal fat and adipocyte size, along with the increase in the glucose transporter GLUT1 expression.

Specie	Model	Treatment %	Results	Reference
S. foetida	Hamsters fed a high-fat and	l 0.5 SO	Reduced:	Major et al., 2008
	0.2% cholesterol diet		Body weight	
			Adiposity	
S. foetida	Leptin deficient ob/ob mice	0.5 SO	Increased:	Ortinau et al.,
			Glucose and insulin tolerance	2012
			Reduced:	
			Liver inflammation	
S. foetida	Obese OLEFT rats	0.5 SO	Reduced:	Ortinau et al.,
			Glucose	2013
			Intra-abdominal fat Dyslipidemia	
			Increased:	
			GLUT1	
S. mexicana	Spontaneously hypertensive	e 0.8 SO	Reduced:	Herrera Meza et
	rats (SHR)		Body weight	al., 2013
			Blood pressure	
			Adiposity	
			Triglycerides	
			Cholesterol	
			Increased:	
			Adiponectin	
S. apetala	Obese Zucker rats	1.3 SO	Reduced:	Reyes-Saldaña,
			Triglycerides	2015
			PPARg	
			Leptin	
S. apetala	Wistar rats fed 30% sucrose	1.15 SO	Reduced:	Morales-Cano,
			Cholesterol	2018
			Triglycerides	
			Adiposity	
			Hepatic steatosis	
S. apetala	Wistar rats fed 30% fructose	1 SO Simultaneous	Prevented: Hypertension	Ramírez-Higuera
			Insulin resistance	et al., 2019
			Hepatic steatosis	
			Adiposity	
			Hypertriglyceridemia	

Table 3: Bioactivities related to metabolic syndrome associated with seeds of Sterculia species.

The preventive and corrective effects of SO from *S. apetala* and *S. mexicana* seeds have been investigated in rat models of MetS, including obese Zucker rats, spontaneously hypertensive rats (SHR), and rats induced to MetS through the ingestion of 30% sucrose or fructose in drinking water. Studies conducted by Herrera-Meza et al. (2013), Reyes-Saldaña (2015), Morales-Cano (2018), demonstrated that SO administration after MetS induction, leads to reductions in body weight, blood pressure, abdominal adipose tissue, adipocytes size, serum levels of triglycerides, cholesterol, insulin, and adiponectin, and an improvement in insulin sensitivity and hepatic steatosis.

In the preventive treatment, where the oil was administered together with MetS induction, rats did not exhibit the alterations observed in those receiving fructose only, including changes in blood pressure, insulin resistance, serum levels of glucose and triglycerides, hepatic steatosis, and body adiposity (Ramírez-Higuera et al., 2019).

Other studies evaluating the effects of SO have shown positive impacts on protein oxidation in the liver and adipose tissue inflammation (unpublished results). Altogether, these findings suggest that SO administration is a promising therapeutic intervention for mitigating the various components of MetS. Further research is needed to fully elucidate the underlying mechanisms and to assess its potential clinical applications.

#### Antioxidant Activity

There exists a close relationship between oxidative stress and chronic inflammatory conditions, both involved in the development of MetS alterations. The endogenous antioxidant system plays a crucial role in preventing degenerative diseases by enhancing the immune response and shielding the body from the detrimental effects of free radicals. In addition, antioxidant compounds help mitigate oxidative stress and alleviate inflammation by neutralizing free radicals and reactive oxygen species, thereby reducing the risk of developing metabolic disorders and related complications (Masenga et al., 2023). In that respect, extracts obtained from *Sterculia* seeds containing bioactive phytoconstituents such as flavonoids, tannins, and phenolic acids, have demonstrated beneficial effects as free radical scavengers, anti-inflammatory agents, and adjuncts in the treatment of conditions including type II diabetes mellitus, obesity, and dyslipidemia (Thabet et al., 2017; Jafri et al., 2019) (Table 4).

Specie	Extract	Compounds/Activity	Reference
S. striata	Methanolic	Phenols and RSA	De Britto Policarpi et al., 2018
S. striata	Methanolic (raw and roaste	d Phenols	Gomes de Moura et al., 2011
	seeds)		
S. apetala	Continuous solid-liqui	d Phenolic compounds and RSA	Mosca et al., 2018.
	extraction water/ethanol		
S. foetida	Oil from seeds	RSA	Bose et al., 2021
S. foetida	Ethanolic	RSA	Jafri et al., 2019
S. setigera	Ethanolic and petroleum ethe	er RAS	Nahla et al., 2018
S. quadrifida	Ethanolic	Flavonoids, phenols and tannins	Dillak et al., 2019
S. murex	Methanolic (roasted seeds)	Phenolic compounds and RSA	Regnier et al., 2017
S. lychnophora	Ethyl-acetate, methanolic an	d Flavonoids and phenols	Tyagi et al., 2024
	aqueous		
S. lychnophora	Aqueous (Polysaccharides)	Ferric reducing antioxidant power and RSA	r Huang et al., 2024
S. scaphigera	Ethanolic	In vivo assays	Dhage et al., 2013
		Increase in superoxide dismutase	2
		and catalase activities	
		Reduction of glutathione levels	
S. scaphigera	Methanolic	RSA	Ogale et al., 2014

**Table 4:** Antioxidant activities of Sterculia's seeds.

RSA: Radical Scavenging Activity

#### Conclusion

The genus *Sterculia* possesses over 200 species, but only a fraction has been studied to date. Notable among these are *S. foetida*, *S. apetala*, *S. mexicana*, *S. lychnofora*, *S. scaphigera*, *S. africana*, *S. urens*, and *S. striata*. While the seeds of this genus have historically been utilized primarily as food or a source of oil, their nutraceutical and pharmacological potential remains largely unexplored. Cyclic fatty acids found in the seed oil have demonstrated efficacy in preventing and treating metabolic alterations associated with MetS in animal models. However, further investigation is needed to describe their mechanisms of action and explore their use in humans. Other compounds present in the seeds, such as phenolic compounds, flavonols, and sterols, exhibit free radical scavenging activity, which could help alleviate the oxidative stress inherent to the chronic inflammation state associated with metabolic syndrome. Furthermore, compounds like alkaloids, polysaccharides, and essential amino acids present in these seeds deserve exploration to assess their potential therapeutic effects.

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