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Sclerocarya birrea: Review of the pharmacology of its antidiabetic effects and toxicity

Abdul Gafar Victoir Coulidiaty[1,2*], Estelle Noëla Hoho Youl[1,3] and Téné Marceline Yaméogo[4,5]

[1]Laboratory of Drug Development, University Joseph Ki-Zerbo, BP 958 Ouagadougou 09, Burkina Faso.
[2]Centre MURAZ, Bobo-Dioulasso, Burkina Faso.
[3]Pharmacology, Clinical Pharmacy and Clinical Toxicology Department, Centre Hospitalier Universitaire Yalgado Ouedraogo, Burkina Faso.
[4]Internal Medicine, Centre Hospitalier Universitaire Sourô Sanou, Bobo Dioulasso, Burkina Faso.
[5]Institut Supérieur des Sciences de la Santé (INSSA), University Nazi Boni, Burkina Faso.

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***Sclerocarya birrea* (A. Rich.) Hochst, an African widespread plant is known to be used for type 2 diabetes management in sub-Saharan Africa. This review aims to summarize the findings for the pharmacology of *S. birrea* antidiabetic effects and its *in vivo* and *in vitro* toxicity. To collate data on *S. birrea*, various scientific search engines like PubMed, Scopus, Scifinder, Google Scholar, Web of Science, Wiley Online, SpringerLink, and ScienceDirect were consulted. The data collected on *S. birrea* were organized in line with antidiabetic pharmacology and toxicology. The plant has shown consistent hypoglycaemic effects attributed to the increase of insulin secretion, glycogenesis and digestive glucose uptake, along with α-amylase and α-glucosidase inhibition. The plant extracts were also associated with the reduction of lipids blood levels, reno- and cardio-protective effects in diabetes mellitus. The extracts exhibited a good safety profile with LD50 ranging from 600 to 3000 mg/kg of body weight depending on the parts used. Several compounds of the extract have been shown to target different receptors involved in glycaemic homeostasis. *S. birrea* which has demonstrated consistent antidiabetic effects and a good safety profile could be investigated in humans in the reverse pharmacology pattern.**

Key words: *Sclerocarya birrea*, type 2 diabetes, antidiabetic, toxicity.

INTRODUCTION

Generally, heterogeneous metabolic disorders are termed diabetes mellitus with chronic hyperglycaemia as its main finding. It can be due to a disturbed insulin secretion or a disturbed insulin effect or usually both (Petersmann et al., 2019). In 2019, the global diabetes prevalence is estimated at 9.3% (that is, about 463 million people), rising to 10.2% by 2030 and 10.9% by 2045. Additionally, prevalence in urban areas is higher (10.8%) than that in rural areas (7.2%), and that of high-income countries (10.4%) exceeds low-income countries(4.0%) (Saeedi et al., 2019). Type 2 diabetes represents 87 to 91% of the global burden of diabetes (Holman et al., 2015; Koye et al., 2018).

Three out of 4 of people with diabetes live in low- and

*Corresponding author. E-mail: gafarvictoir@gmail.com. Tel: +226 70 56 66 23.

middle-income countries. However, the lowest world-standardised prevalence of diabetes in adults was in the Africa Region: 3.8% (Saeedi et al., 2019). Prevention and management of diabetes are of paramount importance. The most essential part of diabetes management includes improving the living standard (diet, exercise, weight reduction, smoking) (Khursheed et al., 2019). The pharmacological management includes oral antihyperglycemics and three injectables which are glucagon-like peptide-1 (GLP-1) (as exenatide), pramlintide and insulin. Currently available oral antihyperglycemics are: biguanides, sulfonylureas (SUs), meglitinides, dipeptidyl peptidase 4 (DPP-4) inhibitors, GLP-1 analogues, thiazolidinedione (TZD), alpha-glucosidase inhibitors and sodium glucose cotransporter inhibitors (SGLT2) (Scheen, 2017; Waring, 2016). In Africa, in addition to the conventional treatments, traditional medicine, which is used by 80% of the populations (Bodeker et al., 2005) offers phyto-treatments for the management of diabetes. These plants are widely used because their low cost, perception of their minimal side-effects, availability and knowledge about their use in the treatment of diseases. Many African plants have been shown to have anti-diabetic effects in animal models (Oguntibeju, 2019). Among which, *Sclerocarya birrea* has shown promising potential. *S. birrea* (A. Rich.) Hochst. (Anacardiaceae), known as marula in English, is a common tree species in the semi-arid, deciduous savannas of sub-Saharan Africa (Viljoen, Kamatou, and Başer 2008; Shackleton et al. 2002); from The Gambia to Ethiopia and Sudan in East Africa (Dimo et al., 2007). *S. birrea* (A. Rich.) Hochst. subsp. birrea is an indigenous fruit tree very widespread in Burkina Faso (Bationo-Kando et al., 2016, 2009). This review reports the connection between experimental pharmacological properties/bioactive compounds and antidiabetic ethnomedicinal uses. Furthermore, as diabetes is a chronic condition, often requiring life time treatment, the toxicological effects were also discussed.

METHODOLOGY

A number of scientific search engines were consulted, including PubMed, Google Scholar, ScienceDirect, Scopus, Scifinder, SpringerLink, Web of Science and Wiley Online. Also, only experimental and analytical studies that investigated the antidiabetic effects of *S. birrea* and/or toxicological effects were included. Review articles, ethnopharmacology and ethnobotany studies were excluded. In this review, data obtained were summarized based on each field, grouped according to themes and arranged in tabular forms for their evaluation.

RESULTS AND DISCUSSION

Pharmacology of *S. birrea* antidiabetic effects

Twelve studies on antidiabetic effect of *S. birrea* were retrieved in PubMed and Google Scholar, none of them were performed in humans. All these studies demonstrated antidiabetic effects. The extraction methods were methanolic, ethanolic, methylene chloride, hexane, acetone and aqueous extraction, the latter being the most frequent. All studies used stem bark extract and one study additionally used root extract. The results are summarized in Table 1.

α-amylase and α-glucosidase inhibition

α-Amylase and α-glucosidase are the key enzymes involved in digestion of dietary carbohydrates. The three key products responsible for α-amylase digestion comprise maltose, maltotriose and α-dextrins. After this, an advanced stage of digestion is observed in the small intestine by α-glucosidase which is a class of brush-border bound enzymes that hydrolyses the terminal α-1, 4-linked glucose residues (Koh et al., 2010; Kim et al., 2016; Hanhineva et al., 2010). By means of transporters, mainly sodium-dependent glucose transporter (SGLT1) that can be found in the brush border membrane at the apical side of enterocytes, cells absorb glucose (Röder et al., 2014). Thus, α-glucosidase and α-amylase inhibition reduces blood glucose levels.

Tree studies demonstrated that *S. birrea* extract inhibits α-amylase and α-glucosidase activities, thus reducing glucose uptake from gut (Mousinho et al., 2013; Mogale et al., 2011; Nkobole et al., 2011). The aqueous and methanol extracts inhibited α-glucosidase and α-amylase activities in a concentration-dependent manner, producing comparable results with acarbose (the positive control) (Mousinho et al., 2013). *In vitro* bioassay results of the α-glucosidase and α-amylase inhibitory activities of the plant extracts demonstrated strong α-glucosidase and α-amylase inhibition at 97.4 ± 0.04% and 94.9 ± 0.01% (Nkobole et al., 2011). Mogale et al. (2011) investigated the *in vitro* inhibitory effects of crude *S. birrea* stem bark extracts against human urinary α-amylase and *Bacillus steatothermophilus* α-glucosidase and found evidence that human urinary α-amylase (> 50%) were more potently inhibited by acetone and methanolic extracts than acarbose ($p < 0.05$). The hexane extract proved to be a weaker inhibitor of α-amylase and a strong inhibitor of α-glucosidase (Mogale et al., 2011). While crude *S. birrea* methanolic extract competitively inhibited α-amylase, there was non-competitive inhibition of α-glucosidase by hexane extracts. All of these lend credence to the idea that polar *S. birrea* metabolites (likely pseudosaccharides) mostly inhibits α-amylase whereas non-polar *S. birrea* metabolites mostly inhibits α-glucosidase (Mogale et al., 2011). In addition, plant polyphenols, which is highly present in *S. birrea* extracts, have been presented as inhibitors of α-glucosidase and α-amylase activities(Havsteen, 1983; McDougall et al., 2005; Matsui et al., 2007).

Table 1. Summary of antidiabetic effects of *S. birrea.*

Authors and years	Extraction methods and parts used	Type of study / model	Results
Youl et al. (2020)	Aqueous ethanolic extracts of leaves	Basal plasma glucose and oral tolerance glucose in mice	(i) The aqueous ethanolic extracts from leaves of Sclerocarya birrea at 100 mg/kg a significant hypoglycaemic effect on basal plasma glucose but significantly reduced ($p<0.001$) peak of hyperglycaemia. (ii) The extract reduced by 36% the glucose level in 3 hours
Perez-Sanchez et al. (2020)	Stem-bark aqueous extract	Analytical study of the compound	*Sclerocarya birrea* stem-bark extracts may be the result of the collective action of multiple bioactive compounds regulating and restoring several dysregulated interconnected diabetic biological processes.
Clementine et al. (2018)	Ethanolic extract trunk bark	(i) Oral temporary hyperglycaemia test in rats (ii) Normoglycemic rats	(i) Hypoglycaemic effects in normoglycemic rats (ii) Antihyperglycemic effects
Ngueguim et al. (2016)	Stem barks aqueous extract	Hyperglycaemia, glucose intolerance, insulin resistance in rats	Hypoglycaemic effect, restored glucose tolerance and insulin sensitivity
Monteomo et al. (2014)	Stem-bark aqueous extract	Hyperglycaemic rat induced by Oral Glucose Tolerance Test	Antihyperglycemic effects 30% at 2h and 40% at 4h
Mousinho et al. (2013)	Aqueous and methanol extracts of the bark	*In vitro*	(i) Inhibited the activities of α-amylase and α-glucosidase (ii) Increased glucose uptake in C2C12, 3T3-L1 and HepG2 cells (iii) Antioxidant activity (iv) Not affect plasma insulin secretion
Youl et al. (2013)	ethanol (80 %) extract of stem barks	Reduction of insulin secretion by INS-1 cells after exogenous oxidative stress	The addition extract to H202 significantly increased insulin secretion compared with H202 alone
Mogale et al. (2011)	Stem bark hexane, methanolic and acetone extracts	In vitro human urinary α-amylase and Bacillus steatothermophilus α-glucosidase	(i) Inhibition of α-amylase (ii) Inhibition of α-glucosidase
Nkobole et al. (2011)	Stem bark acetone extract	α-glucosidase and α-amylase inhibition assays	(i) α-glucosidase Inhibition % (SD): 97.4 ± 0.04 (ii) α-amylase Inhibition % (SD): 94.9 ± 0.01*
Ndifossap et al. (2010)	Stem bark aqueous extracts	(i) Insulin-secreting INS-1E cells and isolated rat islets (ii) Streptozotocin-diabetic rats	(i) Increase glucose-stimulated insulin secretion (ii) Basal insulin release and non-nutrient stimulation was not affected. (iii) Both ATP generation and glucose oxidation were enhanced following the 24-h treatment (iv) In diabetic rats, *Sclerocarya birrea* corrected glycaemia and restored plasma insulin levels after 2 weeks of treatment.
Gondwe et al. (2008)	Stembark ethanolic extract	STZ-induced diabetic rats.	(i) Reduction in blood glucose concentration (ii) Increased hepatic glycogen synthesis (iii) Not affect plasma insulin secretion
Dimo et al. (2007)	Stem bark methylene chloride/methanol extract	Streptozotocin-diabetic rats	(i) Reduction in blood glucose (ii) Increased plasma insulin levels (iii) Improvement in glucose tolerance

Insulinemia increase

Insulin was discovered in Toronto in 1921 by Fredrick Banting and Charles Best (Karamitsos, 2011). Insulin is the dominant anabolic hormone (that promotes dietary carbon source deposition), and its synthesis, quality control, delivery, and action are regulated wonderfully in various organs or “stations” of its bodily journey. Type 2 diabetes is characterized by insulin resistance and insufficient insulin secretion, and type 1 diabetes mellitus, characterized by absolute insulin deficiency (Tokarz et al., 2018; Ruegsegger et al., 2018).

Three studies showed that *S. birrea* increase plasma insulin level as well as its sensitivity both *in vivo* and *in vitro* (Dimo et al., 2007; Ndifossap et al., 2010; Ngueguim et al., 2016). In Ngueguim et al. (2016) study, the plant extract administered in association with supplements in oxidized palm oil and sucrose diet, a significantly ($p<0.001$) increased the insulin sensitivity index by 264.04 and 417.31%, respectively at 150 and 300 mg/kg doses while 10 mg/kg dose of glibenclamide prompted a reduction of insulin constant value by 355.86% when compared with rats receiving hypercaloric diet. They also found that the plant extracts administration with supplements in oxidized palm oil and sucrose diet provoked hyperglycaemia inhibition induced by glucose 1 h after ingestion. The inhibition at the 150 and 300 mg/kg doses was 31.73 and 36.35% ($p<0.001$) respectively compared to the control. In a similar vein, glibenclamide induced hyperglycaemia inhibition by 38.88%. Nevertheless, when plant extract was administered, food intake significantly decreased at 150 and 300 mg/kg doses by 15.95 and 22.29%, respectively whereas 24.55% decrease was provoked by glibenclamide. Finally, the extract of *S. birrea* induced a reduction of glycaemia at a comparable level compared with glibenclamide in diabetes induced rats (Ngueguim et al., 2016).

Dimo et al. (2007) showed that in diabetes induced rats, at the end of 10 h, the plant extract at 150 and 300 mg/kg doses maximally reduced blood glucose concentrations to about 65.8 and 67.0%, respectively, as compared with the basal level. Granted, 10 h after it was administrated, metformin (500 mg/kg) was responsible for the most significant decrease (an 82.4% reduction) in basal glycaemia. In post-prandial hyperglycaemic test, *S. birrea* (300 mg/kg), like metformin (500 mg/kg), significantly reduced blood glucose concentrations 30 and 60 min, respectively after administration, compared to the diabetic control rats (Dimo et al., 2007). Our team obtained similar results. The aqueous ethanolic extract of *S. birrea* leaves at the dose of 100 mg/kg body weight significantly inhibited the hyperglycaemia peak ($p < 0.001$) by 36% in an oral glucose tolerance test with 20% glucose solution in mice fasted for 14 h. However, aqueous ethanolic extracts of *S. birrea* leaves administered to normoglycemic mice reduced plasma glucose by only 0.54%. This suggests a lower risk of hypoglycaemia with either extract in our conditions of use (Youl et al., 2020). *In vivo* studies showed similar results. Following 24 h of treatment at 5 mg/ml, in insulin-secreting INS-1E cells and isolated rat islets, glucose-stimulated insulin secretion was markedly potentiated by the extract (Ndifossap et al., 2010). Similarly, Youl et al. (2013) found that pre-treatment with *S. birrea* ethanol (80%) extract reduce considerably the insulin secretion alteration induces by hydrogen peroxide (H_2O_2) $p< 0.05$). However, two studies showed no effects on plasma insulin level. Evaluation of insulin secretion in RIN-m5F rat pancreatic β-cells showed no alteration (Mousinho et al., 2013). Gondewe et al. (Gondwe et al., 2008) reached to the same results in an *in vitro* evaluation. In non-diabetic rats, plasma insulin secretion was not affected by *S. birrea* extract.

Increase of glucose uptake

The fuel required by most mammalian cells for energy metabolism is supplied by means of glucose transport. Glucose is a very common metabolic substrate that is used both as a fuel and as a signalling molecule (McCall, 2019). Different factors comprising those associated with several aspects of cellular stress regulates glucose transport (McCall, 2019). Glucose uptake depends on a family of eight developmentally regulated glucose transporters, with each having a specific tissue distribution. GLUT 1 has a high affinity for glucose and is insulin independent, being responsible for basal glucose uptake (Beardsall and Ogilvy-Stuart, 2020). One characteristic of diabetes mellitus is glucose homeostasis disruption. Upon food intake, there is increase in blood glucose levels as well as secretion of insulin from pancreatic β cells. As insulin is received, it prompts activation of the insulin signalling pathway in cells possessing insulin receptors, leading to translocation of a glucose transporter (GLUT4), to the plasma membrane, thus expediting glucose influx (Pao et al., 1998; Huang and Czech, 2007; Yoshida et al., 2012). In type 1 diabetes, secretion of insulin is defective, while in type 2 diabetes, cells are insulin resistant (insensitive to insulin), which is likely due to lifestyle. In both cases, cells find it difficult to take up glucose from blood, and as a result, hyperglycaemic situations build up, leading to induction of several diabetic complications (Pao et al., 1998; Huang and Czech, 2007; Yoshida et al., 2012).

Two studies showed that *S. birrea* extracts increase glucose uptake in cells (Mousinho et al., 2013; van de Venter et al., 2008). Venter et al. (2008) measured glucose uptake in Murine C2C12 myoblasts and 3T3-L1 preadipocytes as well as human Chang liver cells. They found that *S. birrea* root, stem and bark induce the uptake of glucose, with the highest performance achieved with the latter. Mousinho et al. (Mousinho et al., 2013)

evaluated glucose uptake in C_2C_{12} myotubes, 3T3-L1 adipocytes and HepG2hepatocarcinoma cells and established that it was significantly ($p < 0.05$) above the positive control (insulin).

Increase of glycogenesis

Glycogenesis is the pathway by which glycogen is synthesized from glucose for storage. Glycogenolysis is a process that deals with glycogen degradation to be utilized as an energy source primarily in liver and skeletal muscle (Patino and Mohiuddin, 2020; Noguchi et al., 2013). Glycogen, which is the main storage form of glucose and prime source of non-oxidative glucose for liver and skeletal muscle, confers significant contributions via its degradation by sustaining normal blood glucose levels and delivering the fuel necessary for muscle contraction (Patino and Mohiuddin 2020). These processes are important to carefully maintain blood glucose levels (Nordlie et al., 1999). Glycogenesis reduces blood glucose levels.

One study showed that *S. birrea* extract promotes glycogenesis in liver. Gondwe et al. measured glycogen in liver tissue of diabetic and non-diabetic rats. *S. birrea* extract at 120 mg/kg significantly increases glycogen level after 5 weeks of administration, as much as metformin 400 mg/100 g of protein, compared with control (110 mg/100 g) and glibenclamide (110 mg/100 g). However, the extract had no significant effect on glycogen levels in non-diabetic rats (850 mg/100 g) compared with (800 mg/100 g), metformin (1100 mg/100 g), glibenclamide (1200 mg/100 mg) (Gondwe et al., 2008).

Chemistry analysis

The Bioinformatics and High Performance Computing Research Group of Universidad Católica de Murcia has recently developed a web server, called DIA-DB, for predicting diabetes drugs that employs two different and complementary approaches: a) comparison by shape similarity against curated database of approved anti-diabetic drugs and experimental small molecules, and b) inverse virtual screening of the input molecules chosen by the users against a set of therapeutic protein targets identified as key elements in diabetes. The protein targets are identified by the DIA-DB for the flavan-3-ols. The docking- and similarity-based outcomes proved that *S. birrea* stem-bark extracts anti-diabetic potential mayresult from the collective action of multiple bioactive compounds regulating and restoring several dysregulated interconnected diabetic biological processes (Pérez-Sánchez et al., 2020). The observed reduction in hyperglycaemia and improvement in the oral glucose tolerance test is possibly attributed to GCK, AMPK, MGAM and AMY2A regulation by the *S. birrea* compounds. AMY2A and MGAM inhibition slows down digestion of carbohydrate and thus lowers the postprandial blood glucose level. Activation of GCK will also lead to a reduction in serum glucose levels by promoting glycogenesis and glycolysis through the phosphorylation of glucose to glucose-6-phosphate (Pérez-Sánchez et al., 2020; Xu et al., 2017). AMPK activation is connected to increased uptake of glucose by the muscles as well as decreased production of glucose by the liver leading to a reduction in blood glucose levels (Pérez-Sánchez et al., 2020; Yan et al.,2013). The observed *in vitro* stimulation of glucose uptake by liver, muscle and adipose cells by *S. birrea* extracts may thus be due to AMPK activation by compound catechin, epigallocatechin, epicatechin, citric acid and gallic acid (van de Venter et al., 2008; Pérez-Sánchez et al., 2020). The incretin hormones half-life will be boosted by DPP4 inhibition thus improving secretion of insulin and allowing time for blood glucose levels to normalize. In a similar vein, potentially-inhibiting HSD11B1 compounds can inhibit production of glucose by the liver and enhance the sensitivity of glucose-dependent insulin (Pérez-Sánchez et al., 2020; Abbas et al., 2019). By inhibiting these receptors, *S. birrea* increase insulin secretion thus reducing blood glucose (Pérez-Sánchez et al., 2020).

Other beneficial effects in diabetes

Antioxidant activity

Under conditions of sustained hyperglycaemia, the oxidative stress is greatly increased. Increased generation of free radical, emanating from glucose auto-oxidation, improved glycation and polyol pathway activity alterations, exerts a modular effect on the oxidative stress level (Araki and Nishikawa, 2010). These free radicals can cause damage to β-cells (Kokil et al., 2010) and the oxidation homeostasis imbalance will develop insulin resistance which is a risk factor for diabetes type 2 (Asmat et al., 2016). Thus, it might be necessary to consider antioxidant therapies targeting precisely the diabetes-induced oxidative stress mechanisms as part of the therapeutic approach towards preventing downstream diabetic complications (Araki and Nishikawa, 2010).

Mousinho et al. (2013) demonstrated that *S. birrea* extract has antioxidant activity. Both the ABTS•+ and DPPH radicals were scavenged by the extracts in a concentration-dependent manner. The *S. birrea* methanol extract gave the lowest IC_{50} value (2.2 µg/ml), suggesting that it has the strongest radical scavenging activity. In both assays, the extract was found to be more potent than Trolox. Armentano et al. (2015) also investigated *S. birrea* methanolic root extract antioxidant activities. Antioxidant activity was measured by 4 different tests (ABTS, nitric oxide (NO), superoxide anion (SO), and β-

carotene bleaching (BCB) assays) and in each one it is demonstrated to be dose-dependent (Armentano et al., 2015). The leaves extract has also shown antioxidant proprieties (Braca et al., 2003). Three compounds (-)-epicatechin 3-O-galloyl ester (10) and (-)-epigallocatechin 3-O-galloyl ester (11) have a Trolox equivalent antioxidant capacity (TEAC) value (~3 mM) higher than that of the reference compound quercetin. Tawi et al. in 2016 showed that water and methanol extracts of bark of *S. birrea* and exhibited excellent antioxidant activities with their 50% inhibitory concentration of DPPH radical ranging from 0.28 - 0.02 to 0.40 - 0.02 µg/ml. This is quite impressive when compared to the positive control vitamin C, which had a 50% inhibitory concentration of 10.62 - 0.87 µg/mL (Tawi et al., 2016).

Youl et al. (2013) also demonstrated that the *S. birrea* protected ß cell viability and functionality against oxidative stress exogenously induced by hydrogen peroxide (H_2O_2). After 2 h, *S. birrea* (10 µg/ml) partially deterred alteration of 50 µM H_2O_2-induced viability. The functionality alteration (insulin secretion) is totally prevented by 1 µg/ml of *S. birrea* after two hours (Youl et al., 2013).

Lipid and cholesterol

People with diabetes mellitus are at an increased risk for cardiovascular diseases, they have more than a 2-fold increased risk of cardiovascular death compared with persons without diabetes. Cardiovascular death accounts for more than 75% of all deaths among persons with diabetes mellitus (Selvin et al., 2004; Khan et al., 2008). Patients with type 2 diabetes often exhibit an atherogenic lipid profile (high triglyceride and low HDL cholesterol) which greatly increases their risk of cardiovascular diseases compared with people without diabetes (Selvin et al., 2004; Windler, 2005). Interestingly, attempts to reduce cardiovascular risks resulted in the improvement of HbA1c even in the absence of any specific intervention targeted at improving glycemic control (Giansanti et al., 1999). Some investigators reported significant correlations between HbA1c and lipid profiles and suggested the importance of good management of diabetes in controlling dyslipidemia (Khan et al., 2008; Ko et al., 1998).

Clementine et al. (2018) evaluated the effect of ethanolic extract of *S. birrea* trunk bark. They found that the triglyceride level in the treated rats decreases. This decrease is very significant ($p < 0.01$), at all doses tested (100, 200 and 300 mg / kg). Similarly, the total cholesterol level decreases. This decrease is highly significant ($p < 0.001$) in all treated rats, regardless of the dose. The analysis shows that the HDL cholesterol level decreases very significantly ($p < 0.01$) at a dose of 100 and 200 mg / kg. This decrease is highly significant ($p < 0.001$) at a dose of 300 mg / kg (Clémentine et al. 2018) Borochov-Neori et al. (2008) demonstrated that the fruit of *S.birrea* also lowers blood lips levels. Three-week administration of the juice as a food supplement to healthy subjects significantly reduced their serum total cholesterol (by 8%), LDL-cholesterol concentration (by 17%), and triglyceride level (by 7%), increased their serum HDL-cholesterol level (by 10%), and attenuated serum oxidative stress (Borochov-Neori et al., 2008).

Toxicology of S. birrea

Nine studies on toxicological effects of *S. birrea* were retrieved in PubMed and Google Scholar, none of them were performed in humans. These studies used aqueous and organic extracts of leave, stem bark, root, kernel and fruits. *In vivo* acute and subchronic studies were performed in rodents and *in vitro* tests in different study-models. Overall, the studies indicated little toxicity of *S. birrea*. The results are summarized in Table 2.

In vivo toxicological investigation of S. birrea

Five studies evaluated acute and subchronic toxicity of *S. birrea* in rodent.

Acute toxicity

No study reported acute toxicity, the LD50 being greater than 500 mg/kg of body weight (Lorke, 1983). Muhammad et al. (2014) reported that LD 50 was greater than 3000 mg/kg body weight in both kernel and fruit peel (Muhammad et al. 2011); Mawoza et al. (2016) estimated that LD50 was greater than 2000 mg/kg (Mawoza, Tagwireyi, and Nhachi 2016); while Baba et al. (2014) reported that LD 50 were 566 and 800 mg/kg body weight for Aqueous and ethanolic extracts of the plant leaves (intra-peritoneal), respectively (Baba et al., 2014). However, some signs appeared at high doses. Behavioural changes in the form of reduced mobility were however noted in the animals given ≥1000 mg/kg of *S. birrea* stem bark aqueous extract (Mawoza et al., 2016). The animals after 24 h of the administration of the aqueous and ethanolic leaves extracts of *S. birrea* show weight loss, increased body temperature and heartbeat and a slight decrease in food consumption (Baba et al., 2014).

Subchronic toxicity

Subchronic toxicity evaluation of *S. birrea* extracts revealed some signs of toxicity. Clementine et al. (2018) found that the extract increased significantly, the urea creatinine, AST, ALT and uric acid suggesting liver and

Table 2. Summary of toxicological effects of *S. birrea.*

Authors and year	Parts used	Models	Results
Mousinho et al. (2013)	Aqueous and methanol extracts of the bark	Cell lines tested; 3T3-L1, C2C12, HepG2 and RIN-m5F viability was assessed using the sulforhodamine B (SRB) assay according to Vichai and Kirtikara	No inherent cytotoxicity in all four cell lines tested, with IC50 values > 100 µg/ml.
Gondwe et al. (2008)	Stembark ethanolic extract	(i) *In vitro* cell culture techniques of the proximal (LLC-PK1) and distal tubule (MDBK) (ii) Kidney functions in rats	(i) Significantly increased GFR with concomitant reduction in plasma creatinine concentration. (ii) Exposure of kidney cell lines of the proximal (LLCPK1) and distal tubules (MDBK) to high doses of *Sclerocarya birrea* decreased cell viability, with proximal cells exhibiting more sensitivity (iii) The high doses (600–1000 mg/ml), however, may not be equivalent to in vivo doses.
Venter et al. (2008)	Root, stem and bark methanol and aqueous extracts	In vitro (Chang liver, 3T3-L1 adipose and C2C12 muscle cells)	Toxicity of the extract Reduction of cell viability
Clementine et al. (2018)	Ethanolic extract trunk bark	Subchronic toxicity of the kidney and liver extract in wistar rats	Extract increases significantly, the urea creatinine, ASAT, ALAT and uric acid
Ndifossap et al. (2010)	Aqueous extracts	(i) cell viability using trypan blue dye exclusion assay; (ii) apoptosis index using ethidium bromide (EB) staining assay and digitonin (30µM) as positive control; (iii) expression of selected genes	(i) This revealed that concentrations up to 10 µg/ml *Sclerocarya birrea* extract did not induce toxic effects (i) Preserved differentiation of INS-1E cells upon *Sclerocarya birrea* extract exposure.
Muhammad et al. (2011)	Kernel aqueous extract of the fruit	Acute and sub-chronic toxicity in rats	(i) No acute toxicity found (ii) LD50 was greater than 3000 mg/kg body weight (iii) No sub-chronic toxicity at 1000 and 2000 mg/kg/day (iv) With 3000 and 4000 mg/kg significant ($p<0.05$) reduction in the body weights were noticed in those administered with and increased in serum total protein, albumin, bilirubin, transaminases, creatinine, urea, uric acid and electrolytes were observed, suggesting liver and kidney toxicity.
Baba et al. (2014)	Aqueous and ethanolic extracts of the plant leaves	Acute toxicity in mice	LD50 were 566 and 800 mg/kg body weight for Aqueous and ethanolic extracts (intra-peritoneal), respectively.
Muhammad et al. (2014)	Peels Extract in Rats extract of the fruit	Acute and sub-chronic toxicity in rats	(i) No cute toxicity shown in terms of mortality and general behaviour changes. (i) LD50 was greater than 3000 mg/kg body weight. Rats fed with 1000, 2000 and 3000mg/kg. (i) Rats fed with 4000mg/kg significantly ($p<0.05$) lower body weight throughout the period of treatment. (i) Significantly ($p<0.05$) higher serum total proteins, albumin, bilirubin, transaminases, creatinine, urea, uric acid and electrolytes were recorded in rats fed with 3000 to 4000 mg/kg, suggesting liver and kidney toxicities
Mawoza et al. (2016)	Stem bark aqueous extract	Acute toxicity and sub-chronic was performed using a single oral administration of 50, 100, 200, 400, 800, 1000 and 2000 mg/kg in rat	(i) Lethal dose is probably higher than 2000 mg/kg (ii) Sub-chronic: animals in the 1000 mg/kg and 2000 mg/kg groups showed a significantly ($p<0.05$) smaller growth rate (iii) Increases in direct bilirubin, total protein, albumin, AST and ALT (iv) Histopathological changes to the liver and kidneys were observed

kidneys toxicity at dose of 100, 200 and 300 mg/kg trunk bark ethanolic extract (Clémentine et al. 2018). Mawoza et al. shown that animals in the 1000 and 2000 mg/kg groups showed a significantly ($p<0.05$) smaller growth rate. This was associated with increases in direct bilirubin, total protein, albumin, AST and ALT supported by histopathological changes to the liver and kidneys. Same results were reported by Muhammad et al.: some subchronic toxicity signs at doses of 4000 mg/kg of peel and kernel extracts. This included reduction in the body weights with an increase in serum total protein, albumin, bilirubin, transaminases, creatinine, urea, uric acid and electrolytes, suggesting liver and kidney toxicity (Muhammad et al., 2011, 2014). However, no subchronic toxicity at doses lower than 2000 mg/kg; which is even higher than then clinical doses.

In the contrary Gondwe et al. described that *S. birrea* stem-bark ethanolic extract has reno- and cardio-protective effects in diabetes mellitus. Daily *S. birrea* treatment (120 mg/kg) for 5 weeks did not significantly affect renal fluid or electrolyte handling in non-diabetic and STZ-induced diabetic rats throughout the experimental period. Chronic *S. birrea* treatment, however, significantly ($p< 0.01$) decreased plasma urea and creatinine concentrations of STZ-diabetic rats with concomitant increase in glomerular filtration rate by comparison with control rats at the corresponding period (0.7 ±0.2 vs. 1.4 ±0.3 ml/min) (Gondwe et al., 2008).

In vitro toxicological investigation of *S. birrea*

The literature has shown contradictory subchronic toxic effects of *S. birrea* extracts. Some studies concluded to reduction in cell viability while others concluded in non-cytotoxicity. Gondwe et al. (2008) investigated the exposure of kidney cell lines of the proximal (LLCPK1) and distal tubules (MDBK) *S. birrea* extract on cell viability. In both cell lines, there was a dose-dependent decrease in cell viability, with significance at the higher concentrations and 48 and 72 h treatments. The LLCPK1 cells were more sensitive to *S. birrea* extract treatment at higher concentrations (600-1000 mg/ml) than the MDBK cells. But, as mentioned by authors, the high doses (600-1000 mg/ml), however, may not be equivalent to *in vivo* doses. In Venter et al. study on Chang liver, 3T3-L1 adipose and C2C12 muscle cells, the organic extracts were found to reduce viability by around 10%, while aqueous extracts had negligeable effects on viability. The root aqueous extracts even increased cell viability by around 5%.

Mousinho et al. (2013) found no cytotoxicity on cell lines tested; 3T3-L1, C2C12, HepG2 and RIN-m5F with IC50 values > 100 µg/mL (Mousinho et al., 2013). Ndifossap et al. (2010) obtained similar results. This revealed that concentrations up to 10µg/ml *S. birrea* extract did not induce toxic effects and preserved differentiation of INS-1E cells upon *S. birrea* exposure (Ndifossap et al., 2010). No data on chronic toxicity were found to support the safety of long terms usage for diabetes management.

Conclusion

Extracts of *S. birrea* show antidiabetic effects in cellular and animal models. These effects are due to the increase of insulin secretion, increase glucose uptake and increase of glycogen secretion. The extracts have also benefits effects in diabetes which include antioxidant activities and reduction of cholesterol and lipid blood levels. These antidiabetic effects are associated with good safety profile. The extract did not exhibit acute nor subchronic toxicity. However, diabetes being a chronic condition, one must be cautious with regard to the lack of data on chronic toxicological effects. In spite of the promising data on antidiabetic effects, today, no study has investigated its effects in humans (Table 1).

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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