Artemisia scoparia and Metabolic Health: Untapped Potential of an Ancient Remedy for Modern Use

Anik Boudreau¹, Allison J. Richard¹, Innocence Harvey¹ and Jacqueline M. Stephens¹,²*

¹ Adipocyte Biology Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA, United States, ² Department of Biological Sciences, Louisiana State University, Baton Rouge, LA, United States

Botanicals have a long history of medicinal use for a multitude of ailments, and many modern pharmaceuticals were originally isolated from plants or derived from phytochemicals. Among these, artemisinin, first isolated from Artemisia annua, is the foundation for standard anti-malarial therapies. Plants of the genus Artemisia are among the most common herbal remedies across Asia and Central Europe. The species Artemisia scoparia (SCOPA) is widely used in traditional folk medicine for various liver diseases and inflammatory conditions, as well as for infections, fever, pain, cancer, and diabetes. Modern in vivo and in vitro studies have now investigated SCOPA's effects on these pathologies and its ability to mitigate hepatotoxicity, oxidative stress, obesity, diabetes, and other disease states. This review focuses on the effects of SCOPA that are particularly relevant to metabolic health. Indeed, in recent years, an ethanolic extract of SCOPA has been shown to enhance differentiation of cultured adipocytes and to share some properties of thiazolidinediones (TZDs), a class of insulin-sensitizing agonists of the adipogenic transcription factor PPARγ. In a mouse model of diet-induced obesity, SCOPA diet supplementation lowered fasting insulin and glucose levels, while inducing metabolically favorable changes in adipose tissue and liver. These observations are consistent with many lines of evidence from various tissues and cell types known to contribute to metabolic homeostasis, including immune cells, hepatocytes, and pancreatic beta-cells. Compounds belonging to several classes of phytochemicals have been implicated in these effects, and we provide an overview of these bioactives. The ongoing global epidemics of obesity and metabolic disease clearly require novel therapeutic approaches. While the mechanisms involved in SCOPA's effects on metabolic, anti-inflammatory, and oxidative stress pathways are not fully characterized, current data support further investigation of this plant and its bioactives as potential therapeutic agents in obesity-related metabolic dysfunction and many other conditions.

Keywords: Artemisia scoparia, diabetes, inflammation, adipocyte, botanical, ethnophamacology
INTRODUCTION

Rising obesity rates around the globe are driving an epidemic of metabolic syndrome (MS) and type 2 diabetes (T2DM), and novel therapeutic interventions are needed. Because the pathogenesis of obesity-related metabolic dysfunction is multifactorial and complex, diverse strategies have been employed to hinder its development and manifestations, namely stimulating insulin production in pancreatic beta-cells, inhibiting hepatic glucose output, reducing glucose reabsorption in the kidney, and enhancing peripheral glucose uptake and insulin sensitivity (1). The molecular mechanisms driving these effects include inhibition of ATP-sensitive potassium channels in pancreatic beta-cells to stimulate insulin release, activation of the glucagon-like peptide-1 (GLP-1) receptor or inhibition of dipeptidyl peptidase-4 activity to stimulate insulin release, activation of the glucagon-like peptide-1 receptor or inhibition of dipeptidyl peptidase-4 activity to enhance incretin signaling and lower circulating glucose levels, and activation of the peroxisome proliferator-activated receptor-gamma (PPARγ) in adipocytes to improve insulin sensitivity in peripheral tissues (2–5). Type 1 diabetes (T1DM), which represents only about five percent of diabetes mellitus cases, results from the progressive destruction of pancreatic beta-cells and consequent inability to produce insulin. Therefore, interventions to improve insulin sensitivity are ineffective for T1DM, and insulin replacement is currently the only glucose-lowering pharmacological treatment available (6). In addition to strategies for controlling glycaemia, treatment of both T1DM and T2DM also includes management of diabetic complications such as kidney disease, cardiovascular disease, and retinopathy.

The first-line medication for T2DM, metformin, is a synthetic derivative of the phytochemical galegine, first isolated from Galega officinalis. This plant, also known as French lilac or goat’s rue, was used medicinally in medieval Europe for many ailments, including symptoms that are now attributed to T2DM (7). Metformin reduces hepatic glucose production via mechanisms that have not been fully elucidated. While it is known that metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK) in the liver, there is evidence that several AMPK-independent mechanisms are likely to be involved in its metabolic impacts (4, 8). These include inhibition of mitochondrial respiration and of the gluconeogenic pathway (8–12). In addition, metformin’s glucose-lowering activity may be partially mediated through effects on the gut (13–15). Therefore, although metformin has been used clinically for over half a century, there is still significant debate around its precise mechanisms of action.

Across the world, plants have been used medicinally for centuries, and many pharmaceuticals are derived from natural products. Even now, factors such as availability, cost, or cultural practices drive the continued use of botanical products as supplements or alternatives to pharmaceuticals. Although rigorous and thorough investigation is often lacking, many plants are currently being screened or studied both in vitro and in vivo to assess their bioactivities and efficacy. One such plant, Artemisia scoparia (SCOPA), has a long history of medicinal use in much of Asia and Central Europe to treat liver diseases, inflammatory conditions, and diabetes, among other ailments. The genus Artemisia comprises hundreds of species, some of which are among the most widely used medicinal plants across the world (1, 2). Perhaps the best known product of the genus is the anti-malarial drug artemisinin, whose isolation from Artemisia annua was awarded the Nobel Prize for Physiology or Medicine in 2015 (3). Other medicinal species include A. capillaris, A. absinthum, A. argyi, A. capillaris and A. dracunculus, but there are many more (4–6). Modern studies have now established that extracts from SCOPA exert a wide range of effects in many cell types and animal models. In addition, many individual bioactive compounds responsible for these effects have been identified. This review describes the traditional folk medicine uses of SCOPA and examines what is currently known about its effects in various animal models and cell types, with a focus on findings relevant to metabolic health. We also discuss individual compounds in SCOPA and their wide range of effects, including the potential to attenuate metabolic dysfunction, particularly in the context of diet-induced obesity. Although SCOPA has not been studied in T1DM, some of its reported actions suggest that it may mitigate diabetic complications in addition to improving glycemic control. Such effects could be beneficial in T1DM as well as T2DM.

Even in the absence of a fully elucidated mechanism of action, identifying additional agents, like metformin, from natural products with therapeutic potential against metabolic dysfunction is of great value in fighting the growing epidemics of obesity, MS, and T2DM. Thus, an overarching goal of this review is to compile and evaluate anecdotal and mechanistic studies of A. scoparia’s ability to modulate metabolic function. We also aim to demonstrate the potential of bioactives from A. scoparia for modern clinical and/or complementary use to support metabolic health, while highlighting the significant need for additional studies to evaluate mechanism(s) of action on a molecular level.

ETHNOPHARMACOLOGY AND TRADITIONAL MEDICINAL USES OF A. SCOPARIA

SCOPA is one of the most widely used medicinal plants across many parts of Asia, and modern ethnobotany studies have documented its many indications in Afghanistan, Pakistan, Saudi Arabia, Iran, and China for conditions such as liver, gallbladder, and digestive disorders; various infectious and inflammatory diseases; ear pain; cardiovascular conditions; and diabetes and hyperglycemia (7–33). One example of the ethnomedicinal documentation of SCOPA is a study conducted in the Upper Neelum Valley of Pakistan, in which data collected from interviews were analyzed and individual plants or medicinal indications were assigned quantitative ethnobotanical indices. SCOPA was determined to have a high use value in this population (21). Reported indications and formulations for SCOPA in traditional folk medicine are shown in Table 1 and Figure 1. It is notable that many of these are common to distinct populations in diverse regions.

SCOPA is very prominent in Traditional Chinese Medicine (TCM), particularly for its hepatoprotective and choleretic effects.
It's uses are extensively described in the canon of TCM literature (41–44) and cited in the current Chinese Pharmacopoeia (35). "Artemisia scopariae herba" (ASH), or "Yinchen", refers to the dried aerial parts of SCOPA or of its close relative, Artemisia capillaris, with the two plants being used interchangeably for its preparation. A decoction of Yinchen is the principal constituent of many TCM formulae, in which ASH is combined with other herbal products. Importantly, a distinction is made between ASH from

| Medicinal Use                      | Region                        | Plant Part | Formulation       | ROA          | Ref(s) |
|-----------------------------------|-------------------------------|------------|-------------------|--------------|--------|
| Diabetes/ Hyperglycemia           | Pakistan/AF border            | Root       | Decoction         | Oral         | (10)   |
| Cancer                            | Pakistan/AF border            | Root       | Infusion          | Oral         | (23)   |
| Hepatitis, jaundice, liver or gallbladder disease | Neelum Valley, Pakistan     | Leaves     | Decoction         | Oral         | (13)   |
| Digestion                         | Neelum Valley, Pakistan       | Aerial parts| Decoction         | Oral         | (23)   |
| Digestion                         | Neelum Valley, Pakistan       | Aerial parts| Decoction         | Oral         | (13)   |
| ENT/Dental                        | Neelum Valley, Pakistan       | Leaves     | Juicce, Decoction | Oral         | (27)   |
| Depurative “blood purification”   | Neelum Valley, Pakistan       | Leaves     | Juice, decoction  | Oral         | (27)   |
| Fever, microbial or parasitic infections, snake or scorpion venom | Neelum Valley, Pakistan | Leaves | Juice, decoction | Oral         | (27)   |
| Burns/wounds/skin/hair            | Neelum Valley, Pakistan       | Leaves     | Juice, decoction  | Oral         | (27)   |
| Cardiovascular                    | Neelum Valley, Pakistan       | Leaves     | Juice, decoction  | Oral         | (27)   |
| Respiratory                       | Neelum Valley, Pakistan       | Leaves     | Juice, decoction  | Oral         | (27)   |

*Yinchen – refers to A. scoparia or A. capillaris.

ROA, Route of Administration.
small Spring seedlings (Mian Yin Chen) and that from flowering plants in late Summer (Yen Chin Hao), each preferable for treating distinct sets of ailments (41, 45). Chemical analyses of ASH have confirmed that its constituents vary greatly depending on the time of harvest (36, 46). While TCM preparations are derived from the aerial parts of SCOPA, the roots of the plant are used in Pakistan (27) and the flowers has been reported in Iran (16).

**EFFECTS OF A. SCOPARIA ON DETERMINANTS OF METABOLIC HEALTH**

**Metabolically Favorable Effects of A. scoparia in Experimental Models of Obesity and Diabetes**

As mentioned above, the use of SCOPA in folk medicine for diabetes and hyperglycemia has been amply documented. A 2016 study found that administration of SCOPA during the second trimester of pregnancy improved insulin sensitivity, fasting plasma glucose levels, and circulating adiponectin levels in patients with gestational diabetes (47). With the exception of that study, SCOPA has not been evaluated in humans for effects on measures of metabolic health such as insulin sensitivity, glycemic control, or cardiovascular risk factors. Likewise, few animal studies have been conducted to examine SCOPA’s metabolically relevant effects. However, in a mouse model of diet-induced obesity (DIO) and insulin resistance, SCOPA administration by gavage or supplementation of diet was found to improve insulin sensitivity as measured by homeostatic model assessment for insulin resistance (HOMA-IR) or insulin tolerance test (ITT) (48–50). Circulating levels of triglycerides, free fatty acids (FFAs), glycerol, and insulin (fasting) were reduced, while adiponectin levels were increased (49–51). In liver, SCOPA supplementation reduced hepatic triglyceride and cholesterol content and enhanced insulin-induced phosphorylation of the signaling proteins insulin receptor substrate (IRS-1), insulin receptor subunit beta (IRβ), protein kinase B (AKT1), and RAC-beta serine/threonine protein kinase (AKT2) (50). Moreover, adenosine monophosphate (AMP)-activated protein kinase (AMPK) activity was enhanced and expression levels of genes involved in de novo lipogenesis were reduced by SCOPA in liver, consistent with the observed improvements in hepatic lipid accumulation (50). SCOPA also had pronounced effects in adipose tissue (AT), where it was shown to robustly enhance insulin-induced phosphorylation of AKT protein in epididymal, but not retroperitoneal or inguinal, white adipose tissue (WAT) depots (49). Levels of monocyte chemoattractant protein 1 (MCP-1), an inflammatory cytokine known to be highly expressed in obesity and insulin resistance, were also significantly reduced in SCOPA-treated animals (48).

**Pro- and Anti-Adipogenic, and Anti-Lipolytic Effects of A. scoparia in Adipocytes**

As described above, an ethanolic extract of SCOPA has metabolically favorable effects in a mouse model of DIO, including improvements in adipose tissue function. This same extract has been shown to enhance adipogenesis of 3T3-L1 cells, a widely used model to study adipocyte differentiation, as measured
by both lipid accumulation and adipogenic gene expression (48). A recent study has revealed that SCOPA can promote adipogenesis in the absence of 3-isobutyl-1-methylxanthine (MIX), a key component in the classic adipocyte differentiation cocktail, and SCOPA significantly induces the expression of several PPARγ target genes, also regulated by MIX, that enhance lipid accumulation during adipogenesis. These data suggest that SCOPA’s adipogenic effects are partially mediated by increased PPARγ activity (52). Another research group investigating individual compounds isolated from a different SCOPA extract reported that 4 of the 19 compounds tested significantly inhibited lipid accumulation in 3T3-L1 cells during differentiation, while other compounds enhanced adipocyte development (53). In this study, no total or parent extracts of SCOPA were tested. A third laboratory observed inhibition of lipid accumulation in 3T3-L1 cells with their crude SCOPA extract as well (54). These apparent discrepancies illustrate three great challenges that accompany the study of botanical extracts: Individual compounds have complex interactions and often fail to mirror effects observed with the parent extracts; plants from different geographic regions, grown in different conditions or harvested at different times of the year may have very different chemical compositions; and variable extraction methods across studies make it impossible to confidently compare results.

Given that obesity drives insulin resistance and diabetes, interventions to reduce fat mass have been pursued as a means to counter obesity-associated metabolic disease. Lowering adiposity through increased energy expenditure or reductions in food intake can indeed have favorable metabolic effects. However, adipogenesis is typically impaired, not enhanced, in obese and insulin resistant states, and limiting adipose tissue expansion in conditions of positive energy balance by inhibiting adipocyte development is generally considered detrimental, as it promotes dyslipidemia and ectopic lipid accumulation (55). This point is underscored by the fact that drugs such as the thiazolidinediones (TZDs), which stimulate adipogenesis via PPARγ activation, are potent insulin sensitizers (56). Since TZDs have fallen out of use in recent years due to significant side effects, efforts are ongoing to identify natural product partial agonists of PPARγ to combat metabolic syndrome (57–60). Researchers investigating SCOPA in adipocytes have employed these alternate strategies (inhibition or promotion of adipogenesis) and have therefore focused on different bioactivities in SCOPA. It should be noted that unlike the pro-adipogenic extract described above, SCOPA extracts that were found to inhibit adipogenesis have not been evaluated in vivo for effects on insulin sensitivity, lipid metabolism, or glycemic control.

Obesity and insulin resistance result in abnormally high rates of lipolysis in the fed state, driven by the impaired action of insulin to inhibit lipolysis, as well as by the chronic inflammation characteristic of obese states (61). As mentioned previously, SCOPA supplementation in the food of high-fat diet-fed mice lowered circulating FFAs and glycerol, consistent with reduced lipolysis rates in adipose tissue (62). In cultured adipocytes, inflammation-associated lipolysis was inhibited in the presence of this same SCOPA extract, indicating that SCOPA has cell-autonomous antilipolytic activity in adipocytes. Interestingly, lipolysis induced by adrenergic stimulation or unstimulated basal lipolysis were not altered by SCOPA (62). A different SCOPA extract has been shown to modestly increase lipolysis in adipocytes under basal conditions but was not tested in inflammatory conditions (63). Given that unstimulated lipolysis rates are very low, this observation may not be relevant in the context of obesity, where inflammatory cytokines drive high lipolysis rates.

### Hepatoprotective Effects of A. scoparia

Liver and gallbladder conditions including jaundice and cholestasis are among the illnesses most commonly treated with Yinchen (A. scoparia or A. capillaris). Research aimed at characterizing these hepatoprotective and choleretic properties has focused mostly on TCM formulations containing Yinchen in combination with other herbs, or on individual compounds isolated from Yinchen, rather than on the Artemisia extracts. However, two studies by Gilani et al. have demonstrated that SCOPA extract could attenuate liver injury induced by acetaminophen in mice (64) or by carbon tetrachloride in rats (65). Hepatic glucose output and lipid metabolism are major contributors to the regulation of circulating glucose and lipid levels, and thus liver function is key in preserving metabolic homeostasis. Likewise, metabolic dysregulation in obesity can lead to ectopic lipid accumulation in liver and non-alcoholic fatty liver disease (NAFLD). It is therefore plausible that beneficial effects of SCOPA in liver could preserve glycemic control and maintain appropriate circulating lipid levels in conditions of hepatic stress or, conversely, protect the liver from the deleterious effects of obesity and insulin resistance. This is supported by the mouse DIO study described above, in which SCOPA improved insulin sensitivity and reduced hepatic lipid accumulation (50).

### Anti-Inflammatory and Antioxidant Effects of A. scoparia

Obesity and T2DM are considered inflammatory states. Infiltration of macrophages and altered resident immune cell populations in adipose tissue promote inflammation and insulin resistance (66, 67). Many conditions treated by SCOPA in TCM or folk medicine have an inflammatory component [(41) and Table 1], and SCOPA has been shown to have anti-inflammatory properties in a wide range of conditions, including inhibition of heat-induced protein denaturation in vitro (68) and reducing inflammatory cytokine production, cell infiltration, and edema in carrageenan-induced acute inflammation in rats and mice (69, 70). Similarly, topical application of SCOPA diminished clinical symptoms, cell infiltration, inflammatory cytokine levels, caspase-1 activity in lesions, and circulating levels of histamine in a mouse model of atopic dermatitis (71). Reductions in markers of adipose tissue inflammation in DIO mice have also been observed with SCOPA supplementation (48, 49). In addition, there are abundant data showing anti-inflammatory actions of SCOPA in cultured cell lines relevant to metabolic function. In lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophages, an ethanolic SCOPA extract, previously found to attenuate lipolysis and markers of adipose tissue inflammation, also inhibited the expression of several...
inflammatory genes (72). In this same cell line, a different ethanolic extract reduced nitric oxide (NO) production in cells treated with LPS and interferon gamma (IFNγ) (53), while a methanolic extract from a third source failed to inhibit NO release from LPS-treated RAW 264.7 cells (63). Although the reason for this discrepancy cannot be ascertained, the three studies investigated extracts prepared from different plant material originating from diverse geographic locations, using various extraction methods and solvents, and tested at different doses; one or more of these factors could explain these seemingly conflicting results. Similar studies were conducted in isolated bone marrow-derived macrophages (BMDM) from mice, in which NO, inducible nitric oxide synthase (iNOS), and inflammatory cytokine levels were all reduced by SCOPA treatment in stimulated cells (69). Comparable effects of SCOPA have been observed in the THP-1 human monocyte cell line, undifferentiated 3T3-L1 murine preadipocytes, and in the HMC-1 human mast cell line (69, 73). Moreover, reduced pro-inflammatory NF-κB promoter activation in IL-1β-treated pancreatic beta-cells, which are also vulnerable to obesity-related inflammation, has been observed in response to SCOPA (72). Taken together, these data from multiple models and treatment conditions clearly indicate that SCOPA is a potent anti-inflammatory agent and that it can antagonize inflammation in conditions consistent with metabolic dysregulation.

Oxidative stress plays an important role in insulin resistance, the progression to diabetes, and diabetic complications. Indeed, hyperglycemia induces the production of reactive oxygen and nitrogen species, and the resulting oxidation of lipids, proteins, and DNA mediates diabetic complications such as neuropathy, nephropathy, retinopathy, and vascular damage. Although oxidative stress occurs in response to hyperglycemia, it can also drive metabolic dysfunction, as it hinders insulin signaling and glucose uptake in cultured adipocytes, myocytes, and vascular smooth muscle cells (74–80). Mechanisms involved in these effects have been attributed to mitochondrial dysfunction, inhibition of insulin signaling proteins, and negative modulation of the expression and translocation of the glucose transporter GLUT-4 [reviewed in (80)]. Furthermore, reactive oxygen species (ROS) have a range of deleterious effects on pancreatic beta-cell function, including increased apoptosis, reduced beta-cell neogenesis, mitochondrial dysfunction, and impaired insulin secretion (78, 81). Finally, oxidative stress can contribute to insulin resistance by activating inflammatory pathways (80). Essential oils and extracts of SCOPA have been reported to have antioxidant and free radical-scaping properties (82–85), which could be consistent with improvements in metabolic function. Studies and reviews of SCOPA’s anti-inflammatory and antioxidant effects are shown in Table 2.

**Cardiovascular Effects of A. scoparia**

Metabolic syndrome is a cluster of risk factors for cardiovascular disease and diabetes. Obesity, insulin resistance, and diabetes promote hypertension, hyperlipidemia, and vascular damage, thereby increasing risks of coronary artery disease, stroke, and peripheral vascular disease. SCOPA has been used as an anti-hypertensive, a vasodilator, and an anti-hypercholesterolemic agent in traditional medicine (Table 1), and data from modern studies have been consistent with these historical uses. As is the case for SCOPA’s hepatoprotective properties, investigations have focused on SCOPA-containing TCM preparations or on single compounds isolated from SCOPA, but Cho et al. have shown that diet supplementation with an aqueous SCOPA extract lowered blood pressure and produced other favorable effects in spontaneously hypertensive rats (88). Beneficial effects included reductions in angiotensin converting enzyme (ACE) activity, angiotensin II (AngII) levels, and lipid peroxidation in serum. Given these observations, it is plausible that SCOPA’s effects on the cardiovascular system could mitigate some of the complications of metabolic syndrome or diabetes. Studies showing cardiovascular effects of SCOPA appear in Table 2.

**EFFECTS OF BIOACTIVE COMPOUNDS FOUND IN A. SCOPARIA**

**Coumarins**

SCOPA is rich in plant coumarins (93). The three related coumarins scoparone (6,7 - dimethoxy coumarin), scopolein (7-hydroxy-5-methoxy coumarin), and esculetin (6,7 - dihydroxy coumarin) are found in many Artemisia species and

---

### TABLE 2 | In vitro and in vivo studies of A. scoparia.

| Extract                  | Metabolic Complications | Cardiovascular/ dyslipidemia | Hepatic dysfunction | Cancer | Inflammation/ oxidative stress | Neurological/ Behavioral | Anti-microbial | Renal |
|--------------------------|-------------------------|------------------------------|---------------------|--------|-------------------------------|--------------------------|----------------|-------|
| Ethanol extract          | (48–50, 62, 72, 86)     | (62)                         | (63)                | (63)   | (68, 84)                      | (58, 90)                 | (82, 91)       | (92)  |
| Methanol extract         | (63)                    |                              | (83, 87)            | (68, 69)| (69)                          | (83, 90)                 | (68, 69)       | (83)  |
| Aqueous Extract or fraction | (89)                  |                              |                     |        |                               |                          |                |       |
| Flavonoids               |                         |                              |                     |        |                               |                          |                |       |
| Total flavonoid          |                         |                              |                     |        |                               |                          |                |       |
| Essential oil            |                         |                              |                     |        |                               |                          |                |       |
| DCM* extract             |                         |                              |                     |        |                               |                          |                |       |
| Commercial extract, n.s. | (47)                    |                              |                     |        |                               |                          |                |       |
| Crude extract            | (54)                    |                              |                     |        |                               |                          |                |       |
| Whole extract, n.s. or butanol fraction | (65)                  |                              |                     |        |                               |                          |                |       |

*DCM, dichloromethane.  
*n.s., Not specified.
are considered major components of SCOPA (36, 41). Many coumarins have potent anti-inflammatory or antioxidant effects that account for a wide range of bioactivities (94). In addition, natural and synthetic coumarins are under investigation as promising treatments for many conditions, cancer in particular (95–102). The therapeutic potential of these coumarins is supported by molecular docking analyses (94, 103–112) and structure-activity relationship (SAR) studies (111, 113–117).

**Scoparone**

Scoparone, a prominent compound in TCM preparations, has long been known to have hypotensive and vasodilatory properties (118) and has been found to have several additional favorable cardiovascular effects, including inhibition of ACE activity in vitro (126) and reduction in AngII-induced myocardial changes in rodents, cultured myocytes, and cardiac fibroblasts (127, 128). Furthermore, there is evidence that scoparone can mitigate cardiac ischemia/reperfusion injury in vitro and in vivo settings (129).

Scoparone also has anti-atherogenic effects including the inhibition of vascular smooth muscle cell proliferation and migration (130, 131), inhibition of platelet aggregation (132), and the attenuation of atherosclerotic plaque formation and dyslipidemia in hyperlipidemic diabetic rabbits (133, 134). One study also found that scoparone decreased peroxisome proliferator-activated receptor gamma (PPARγ) activity, expression of PPARγ target genes, and lipid accumulation in differentiating 3T3-L1 adipocytes (135). In cultured rat mesangial cells, high glucose-induced production of extracellular matrix proteins was reduced with scoparone treatment (136), a finding with potential implications for renal diabetic complications.

As is the case for SCOPA extracts and traditional preparations, hepatoprotective effects have been reported for scoparone in NASH (137, 138) and in conditions of hepatotoxicity or liver injury induced by carbon tetrachloride or alcohol (139–141). Consistent with folk uses of SCOPA in the treatment of jaundice and cholestasis, scoparone also promotes bilirubin clearance through activation of the constitutive androstane receptor (CAR) (142). Interestingly, CAR activation has been shown to improve insulin sensitivity, glucose metabolism, and hepatic lipid accumulation in leptin-deficient ob/ob mice (143), and to prevent obesity, insulin resistance, and hepatic steatosis in HFD-fed mice (144). CAR agonism has been proposed as a therapeutic target for obesity, insulin resistance, and diabetes (142–146). In a recent study, a panel of natural and synthetic coumarin derivatives was screened for the ability to activate CAR, and scoparone was found to improve glucose tolerance in leptin receptor-null db/db mice (147).

Anti-inflammatory and antioxidant properties of scoparone have been demonstrated in a wide range of conditions, and some of the pathways impacted by these effects have been described. Studies in the murine RAW 264.7 macrophage cell line demonstrated that scoparone could attenuate the LPS- or IFNγ-induced production of inflammatory cytokines, as well as iNOS and cyclooxygenase 2 (COX2) protein levels and corresponding NO and prostaglandin E2 (PGE2) release (148). Similar results were obtained in a human monocyte cell line, in which scoparone attenuated phorbol-12-myristate-13-acetate (PMA)-induced inflammatory cytokine production by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation (149).

In a mouse model of acute lung injury, pulmonary edema, histological changes, and LPS-mediated inflammatory cytokine production were improved by scoparone in vivo, while in vitro experiments in alveolar macrophages revealed that the compound’s anti-inflammatory effects were mediated through the toll-like receptor 4 (TLR4)/NFκB pathway (150). Anti-inflammatory effects of scoparone in a rat model of colitis have also been reported (151), while in BV2 microglial cells, scoparone attenuated LPS-induced neuroinflammatory responses by blocking interferon regulatory factor 3 (IRF3) and extracellular signal-regulated kinase (ERK) activation (126). In a mouse model of acute seizures, scoparone preserved blood-brain barrier integrity, prevented inflammation and apoptosis, and inactivated the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway in vivo. This same study determined that scoparone could also inhibit astrocyte activation elicited by LPS (152).

In addition to interfering with inflammatory pathways, scoparone has been shown to provide protection from oxidative stress, as demonstrated in 2,2-diphenyl-1-picrylhydrazyl (DPPH) and lipid peroxidation assays in vitro (151, 153), and to inhibit production of ROS and preserve antioxidant enzyme activity in response to several types of oxidative stressors (154, 155). Antioxidant activity has also been implicated in scoparone’s ability to protect against kidney damage elicited by the chemotherapeutic agent cisplatin (156), to reduce markers of pancreatic fibrosis in cultured pancreatic stellate cells (157), and to prevent osteoclast differentiation and bone resorption in vitro (158).

Effects of scoparone have been observed in many other systems and models, including immunosuppressive functions associated with autoimmunity, allergies, and graft rejection (159, 160); neurite outgrowth and dopamine synthesis and release in the PC12 neuronal cell line (161–163); proliferation and migration of cancer cells (105, 164); bactericidal, antifungal, and antiparasitic properties (165–167); promotion of melanogenesis; and activation of the cystic fibrosis transmembrane conductance regulator (CFTR) (168, 169). Table 3 presents a summary of the wide range of bioactivities attributed to scoparone.

**Scopoletin**

Scopoletin is a naturally fluorescent compound found in many plants (191, 214, 215, 246). It is a substrate for peroxidases, which convert scopoletin to non-fluorescent compounds, and has thus been widely used for many decades, in combination with horseradish peroxidase, as the basis for high-sensitivity hydrogen peroxide detection assays (495–498). Several studies have demonstrated scopoletin’s antioxidant capabilities in vitro, using common cell-free methods such as the DPPH, Trolox equivalent antioxidant capacity (TEAC), ferric reducing ability of plasma (FRAP), or beta-carotene/bleaching assays, while superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite are among the reactive species shown to be effectively scavenged by scopoletin (114, 180, 216–223, 247). Hepatoprotective antioxidant effects of scopoletin have also been observed in cultured HepG2 cells and primary hepatocytes (154, 200),
however one study failed to detect significant antioxidant activity for scopoletin (499).

Given the important role of oxidative stress in the etiology of numerous disorders, it is not surprising that some of scopoletin’s favorable effects in disease states are attributed to its antioxidant properties. For example, scopoletin has been reported to have antioxidant effects in hyperthyroid-induced hyperglycemia in rats (224), as well as in oxidant-induced hemolysis of rat erythrocytes (225). The brain is particularly vulnerable to oxidative stress, which is known to be central to many neurodegenerative conditions (500). A study performed in mouse brain homogenates revealed that scopoletin strongly inhibited the oxidative protein modifications induced by copper (226), which can contribute to the pathologies associated with atherosclerosis, Alzheimer’s disease (AD), and Wilson’s disease (501–503). A recent study examined several aspects of oxidative stress involved in the pathogenesis of Parkinson’s disease (PD) and showed that scopoletin attenuated depletion of cellular reduced glutathione or ATP, inhibited ROS generation, and prevented cell death in oxidative conditions in vitro (227). These findings were extended to a Drosophila mutant model

| TABLE 3 | In vitro and in vivo effects of bioactive compounds found in A. scoparia. |
| Compound | Metabolic Complications | Cardiovascular/ dyslipidemia | Hepatic dysfunction | Cancer | Inflammation/ oxidative stress | Neurological/ Behavioral | Anti-microbial | Renal | Reproduction | Asthma/ Allergy | Other |
|----------|--------------------------|-----------------------------|-------------------|-------|-----------------------------|-------------------------|----------------|-------|--------------|--------------|-------|
| **Coumarins** | | | | | | | | | | | |
| Scoparone | (132–136, 147) | (119, 122–134) | (137, 138, 140, 142, 154, 170–174) | (105, 164) | (149–151, 153–155, 157, 175, 176) | (126, 152, 161–163) | (165–167) | (136, 158) | (177) | (158, 160, 175) | (178) |
| **Scopoletin** | (108, 116, 180–190) | (126, 132, 191–199) | (154, 200–202) | (97, 203–213) | (114, 154, 214–245) | (106, 109, 110, 227, 246–264) | (165, 265–278) | (279) | (175, 251, 280–288) | | |
| **Escoletin** | (116, 180, 259–312) | (303, 313–317) | (139, 171, 318–320) | (96, 321–349) | (226, 307, 318, 350–368) | (111, 367–372) | (165, 373–375) | (107, 339, 376–378) | (379) | (282, 354, 380–383) | |
| **Flavonoids** | | | | | | | | | | | |
| Flavone | (57, 390–397) | (395, 398–402) | (395, 403, 404) | (395, 405, 406) | (395, 407) | (393, 395) | (395, 408) | (395) | (396, 409) | | |
| Rutin | (394, 397, 410–416) | (402, 417) | (412, 415, 418–421) | (422, 423) | (419, 420, 424, 425) | (418, 420) | (417) | (421) | (412, 429) | (429) | (437) |
| Flavanones | (426–429) | (427, 430, 431) | (432) | (427, 433) | (427, 428, 434) | (435, 436) | (450) | (451) | (452) | | |
| **Chromones** | | | | | | | | | | | |
| Capillarisins | (116) | (438, 439) | (440–443) | (444–449) | (448) | (450) | (451) | (452) | | | |
| **Phenolic Acids** | | | | | | | | | | | |
| Chlorogenic Acids | (453–455) | (455–458) | (459) | (460, 461) | (71, 73, 222, 462–464) | (465–467) | (488–470) | (492) | (493) | (489) | (494) |
| Prenylated coumaric acids | (472–477) | (475–485) | (464, 472, 486–489) | (490, 491) | | | | | | | |

| aMelanogenesis. |
| bOsteoprotection. |
| cRespiratory. |
| dAging and healthspan. |
| eGastrointestinal. |
| fOphthalmic. |
| gCartilage or muscle. |
| hQuercetin and isorhamnetin. |
| iNaringenin and blumeatin. |
| jCaffeic acid, dicaffeoylquinic acids, Chlorogenic acid. |
| kArtepillins, capillartemisins, drupanin, scopo-coumarins. |
| lHypoxia/ischemia. |

Boudreau et al. Health-Promoting Properties of Artemisia scoparia | Frontiers in Endocrinology | www.frontiersin.org | February 2022 | Volume 12 | Article 7270618
of PD, where scopoletin treatment reduced accumulation of mitochondrial ROS and promoted recovery from degenerative phenotypes (227). Several other studies have shown that scopoletin can prevent oxidative injury in models relevant to diseases such as PD and AD. These include prevention of oxidative injury and induction of antioxidant gene expression in HT-22 and SH-SY-5Y cells (248, 249), as well as inhibition of monoamine oxidase activity (106, 250).

One important contributor to oxidative stress in many cell types is the xanthine oxidase (XO)/xanthine dehydrogenase (XDH) system (201, 504, 505). XO activity in the liver produces uric acid, which is released into circulation and excreted by the kidney. Hyperuricemia, due to excessive uric acid production in the liver or impaired clearance in the kidney, causes accumulation of uric acid crystals in joints (gout) and in the kidney. Scopoletin shows inhibitory activity in enzymatic assays of XO in vitro (506). Additionally, scopoletin administered either by intraperitoneal injection or by oral gavage of scopoletin-loaded micelles was shown to correct hyperuricemia in mice through two separate mechanisms, namely inhibiting hepatic XO activity and enhancing uric acid excretion by the kidney (201, 202). Notably, XO activity is associated with obesity-related metabolic dysfunction, and XO inhibitors typically prescribed for gout or hyperuricemia are proving to be effective in mitigating cardiovascular and renal complications of diabetes (504, 507, 508).

In addition to antioxidant effects, scopoletin has potent anti-inflammatory activity. Numerous studies have demonstrated the ability of scopoletin to diminish the production of proinflammatory mediators such as cytokines and eicosanoids in many cell types, including macrophages, mast cells, fibroblasts, and platelets (228–237). In vivo effects of scopoletin in rodent ear or paw edema models and in models of inflammatory conditions such as arthritis, gastro-esophageal disease, gastric ulcers, gout, pleurisy, pancreatitis, as well as nociceptive or analgesic properties, have also been described (215, 237–242, 291, 509, 510). Mechanisms involved in scopoletin’s anti-inflammatory effects include negative regulation of inflammatory signaling pathways and inhibition of lipoxigenase and cyclooxygenase enzyme activities (214, 239, 243, 247, 280, 281). Scopoletin’s anti-inflammatory properties have also been implicated in its effects on various pathologies, particularly in the realm of immunity, as it has been shown to regulate complement pathway activation, mast cell degranulation, as well as several aspects of innate, humoral, and adaptive immune function, suggesting potential roles in allergies, asthma, and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (175, 251, 282–288, 511).

Scopoletin has been studied in several models of neurological dysfunction and has an array of favorable effects. Some of these are at least partly attributable to its antioxidant or anti-inflammatory properties, like reducing inflammation-induced anxiety in mice or attenuating neural deficits, brain edema, and inflammatory cytokine production in intracerebral hemorrhage in rats (252, 253). In addition, several groups have demonstrated scopoletin’s ability to inhibit acetyl- and butyryl-cholinesterases in vitro (110, 247, 254–257, 512) and in vivo (258). Antidepressant, anti-psychotic, and anti-amnesic effects were also observed in behavioral studies in mice (246, 258–261). A study investigating anticonvulsant effects of *Benkara malabarica* (Linn.) root extract found that scopoletin inhibited GABA transaminase activity (262). Consistent with this finding, molecular docking analysis has demonstrated affinity of scopoletin for both GABA transaminase and for the GABA-A receptor (252). The anticonvulsant drug vigabatrin is an irreversible inhibitor of GABA-T, and there is convincing evidence that it is effective in attenuating anxiety symptoms (513). Formation of amyloid beta peptide 42 (Aβ42) and α-synuclein fibrils, processes central to the pathogenesis of AD and PD respectively, have both been shown to be inhibited by scopoletin (109, 110). These actions are likely complementary to the antioxidant mechanisms described above (227) in combatting neurodegenerative diseases. Finally, scopoletin improves neuronal plasticity, as measured in ex vivo electrophysiological assays, and exerts neuroprotective activity in a rat spinal cord injury model (263, 264).

In conditions related to metabolic health, scopoletin acts favorably on many pathways in vivo, as well as in various cell types and experimental conditions. In animal models of diet-induced obesity, diabetes, or alcohol-induced metabolic dysfunctions, scopoletin restored insulin sensitivity, reversed disruptions in circulating lipids, glucose, insulin, and inflammatory cytokines, while also attenuating lipid accumulation and fibrosis in liver, restoring adiponectin levels in white adipose tissue, and reducing oxidative stress in the pancreas (181–187). Consistent with these *in vivo* observations, scopoletin has been shown to mitigate insulin resistance and improve metabolic functions in cultured hepatocytes, adipocytes, and pancreatic beta-cells (184, 185, 188, 514). *In vitro* assays have revealed that enzymes involved in glucose homeostasis (protein tyrosine phosphatase 1b, α-glucosidase and α-amylase) or in diabetic complications (aldose reductase) are inhibited by scopoletin (108, 116, 180, 184, 187, 189, 190). While effects described above are likely to improve cardiovascular health in the context of metabolic syndrome, scopoletin also acts directly on the heart and vasculature. Scopoletin has antihypertensive actions (126, 191–193), anti-atherosclerotic capabilities (132, 194–196), and vascular spasmylic/vasodilatory effects (191, 193, 197–199).

Scopoletin is a compound of interest in cancer research, as it has been shown to have apoptotic, cytotoxic, anti-proliferative, anti-angiogenic, and anti-metastatic activities in various cancer cell lines (97, 203–212). Efforts are ongoing to develop synthetic derivatives of scopoletin and to characterize and improve its bioavailability and pharmacokinetic properties (96). Finally, a handful of other bioactivities have been reported for scopoletin, among them the promotion of melanogenesis (296–298) and osteoprotective (292, 293), antitussive (515), gastrokinetic (294), and antimicrobial properties (165, 265–278, 516), as well as anti-aging effects in skin and lung fibroblasts (289, 290).

It is notable that many of the same signaling pathways are modulated by scopoletin across the wide variety of experimental models and conditions in which it has been investigated. Scopoletin can activate the AMPK pathway (181, 182, 186, 263, 514) and the PI3K/AKT pathway (184, 186, 188, 514), and inhibit the inflammatory TLR4/myeloid differentiation factor 88 (MyD88) and NF-κB pathways (94, 181, 183, 233,
237, 241, 251, 252, 517, 518). There is also substantial evidence that scopoletin can inhibit the MAPK pathway in a variety of cell types (199, 235, 237, 241, 252, 290, 297).

**Esculetin**

Like scoparone and scopoletin, esculetin’s well-documented antioxidant and anti-inflammatory properties are central to its beneficial effects in biological systems (226, 350–355, 384, 519). A broad range of inflammatory or oxidative conditions have been shown to be impacted by esculetin. These include lung injury and fibrosis (356, 357, 520); fibromyalgia (521); neuronal oxidative stress (522); psoriasis (523); arthritis (358); nociception (359); colitis (360); allergy, immunity, and asthma (282, 354, 380–383); and sepsis (361). The effects of esculetin on numerous cancer cell types have been extensively studied (94, 321–342, 519, 524, 525) and are the basis for efforts to develop novel anticancer agents (98, 341). Neuroprotective and behavioral actions of esculetin have also been described (111, 299, 367–371, 526–528). Selected publications highlighting these effects of esculetin are featured in Table 3.

**Flavonoids and Chromones**

Flavonoids are highly abundant compounds in all plants; they are extensively studied for various bioactivities and have a wide range of effects in many biological systems. Numerous flavonoids have been identified in SCOPA, however their relative abundance varies widely among plants and extracts from different sources (36, 41). Since there exists abundant literature regarding the bioactivities of flavonoids, we will present only a subset of the most commonly reported, most abundant, or most thoroughly investigated flavonoids in SCOPA. As a representative example, cirsimaritin has been shown to have anti-proliferative, anti-metastatic, and anti-carcinogenic effects in cancer cell lines (529–534), diabetes- and metabolism-related effects (535–537), as well as anti-inflammatory, antioxidant, and antimicrobial properties (538–543). Studies have also demonstrated that cirsimaritin can modulate neurological, immune, and digestive functions (544–548), and attenuate renal injury (549, 550). Additional activities of selected flavonoids are shown in Table 3.

The chromone capillarisin is known as a major constituent of *Artemisia capillaris*. It is also relatively abundant in SCOPA but is not known to be a bioactive constituent of other plants. There are multiple reports of anti-inflammatory and antioxidant effects of capillarisin (444–448, 551), which has also been shown to inhibit tumor cell invasion, inhibit signaling transducer and activator of transcription 3 (STAT3) activation, slow cell growth, and promote apoptosis in various cancer cell lines (440, 441, 443, 552). Other reported effects of capillarisin include anti-asthmatic activity (451) and promotion of penile erection in a rabbit model (450). Studies of capillarisin and its derivatives that are found in SCOPA are summarized in Table 3.

**Phenolic Acids**

Chlorogenic acid, caffeic acid, 3,5-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid are related phenolic acids found in many plants or, in the case of caffeic acid, all plants. Chlorogenic acid and its derivatives are abundant in SCOPA and have been shown to mediate some of SCOPA’s effects (71, 73, 85). Unlike the ubiquitous chlorogenic acid derivatives, prenylated coumaric acids (PCAs) are not common in plants, and the most thoroughly characterized of these compounds, artepillin C, druparin, and baccharin, have been primarily studied from Brazilian green propolis (476, 553–555). The most prominent bioactivities of chlorogenic acids and PCAs are presented in Table 3. Although not all studies of SCOPA’s chemical constituents have detected PCAs, capillartemin B and druparin have been identified in SCOPA (53, 556–558), and additional PCAs have been reported in *Artemisia capillaris* (559, 560). PCAs are not considered major constituents of SCOPA, however several of them have been isolated from a SCOPA extract with potent adipogenic activity (556, 557). Fractions of this extract that were most effective in promoting adipogenesis were rich in PCAs, and activity was confirmed for three PCAs isolated from these fractions, including two co-purified isomers of a novel PCA, termed “cis-scopa-trans-coumarin” and “cis-scopa-cis-coumarin”. Like the PCAs from SCOPA, PCAs from propolis can activate PPARγ, promote adipocyte differentiation, and mitigate obesity-associated metabolic dysfunction (472–474, 561–563). Given that these compounds have not been reported in SCOPA extracts found to inhibit adipogenesis, the presence or absence of PCAs is a plausible explanation for the seemingly divergent effects of SCOPA on adipocytes in studies using different extract preparations. Interestingly, a unique enzyme has recently been isolated from *A. capillaris* that catalyzes two successive prenylations of p-coumaric acid to yield artepillin C, with druparin as a mono-prenylated intermediate (564). It appears likely that an equivalent enzyme may exist in SCOPA and in other plants that synthesize these compounds.

**BRIDGING THE GAP: SCOPA AS A MODERN INTERVENTION TO PROMOTE METABOLIC HEALTH**

We have reviewed multiple lines of evidence for metabolic benefits of SCOPA. However, these data have emerged in a piecemeal fashion, and comprehensive studies to adequately assess SCOPA as a therapeutic or preventive intervention for metabolic dysfunction are lacking. One ethanolic SCOPA extract has been shown to have beneficial effects on adipose tissue function, hepatic lipid accumulation, and insulin sensitivity in a mouse model of DIO (48–50), and a different extract was found to attenuate gestational diabetes in a small human study (47). Ethnopharmacological data, as well as the broad range of bioactivities of SCOPA observed in various cell lines and disease models, also provide strong rationale to investigate SCOPA in humans with obesity or metabolic syndrome. The widespread medicinal use of SCOPA in many parts of the world suggests favorable safety and toxicity profiles, however these have not been formally studied, and such data will be needed in the assessment of SCOPA’s potential as a therapeutic intervention. For example, since SCOPA is known to affect hepatic function and to increase whole-body insulin sensitivity in mice, adverse effects in the liver or risk of hypoglycemia are potential concerns. Given the high variability in the chemical composition of SCOPA extracts, their rigorous characterization, using unbiased and standardized methods will also be crucial in interpreting results from different
extracts and in guiding pharmacokinetic evaluation of potential therapeutic extracts. In our view, details of extract composition reported for SCOPA are generally insufficient, and greater efforts are required to characterize extracts that are being studied for the promotion of metabolic health. Repositories of serum and tissue samples from in vivo studies would also be helpful in laying the groundwork for pre-clinical or translational studies. Differences in biological effects and chemical composition among various SCOPA preparations could also serve as a resource for correlating constituent compounds with bioactivity. SCOPA’s reported hepatoprotective and antioxidant properties, as well as its beneficial effects on cardiovascular parameters are consistent with favorable metabolic effects but have not been investigated in the context of human metabolic disease. In addition, SCOPA’s potential effects in many cell types and experimental models relevant to obesity or metabolic syndrome have not yet been interrogated. These include measures of insulin sensitivity or glucose uptake in skeletal muscle cells, glucose output from hepatocytes, and insulin secretion from pancreatic beta-cells. SCOPA’s ability to mitigate diabetic complications is also unknown, although its documented antioxidant and anti-inflammatory effects suggest that it may protect against the consequences of chronic hyperglycemia. All these aspects of SCOPA bioactivity merit more systematic assessment in conditions of metabolic dysfunction. Finally, mechanisms responsible for SCOPA’s pleiotropic actions remain only partially explored. As described in this review, SCOPA or its constituent compounds have been shown to regulate various signaling pathways or enzyme activities, but the molecular players, mechanistic details, and implications of these effects remain to be elucidated. Thus, a wide range of experimental observations offer promising evidence of SCOPA’s metabolic benefits, but critical pieces of data are needed to realize its full promise as a bona fide therapeutic.

CONCLUSION

The historical and anthropological importance of botanicals in health and disease is unquestionable. Not only are plants used in folk medicine applications around the world, but they are also consumed as nutritional supplements and are the origin of many modern pharmaceuticals. Despite the successes of synthetic drug development, there is great value in investigating complex botanical extracts for several reasons. First, there is a need to characterize and evaluate botanicals in current use. A cross-sectional study conducted between 2002 and 2012 reported that 18% of adults in the US use dietary supplements (565). According to the American Botanical Council, sales of herbal supplements topped 8.8B$ in 2018 and were on the rise (abc.herbalgram.org). This market is largely unregulated, and rigorous studies addressing the safety, modes of action, and efficacy of such supplements are desirable. Second, synergistic interactions between phytochemical compounds are common, and individual constituents often fail to recapitulate activities of their parent botanical extracts (566, 567). Third, the thorough study of complex botanical extracts enables the identification of novel and unique lead compounds that may not otherwise emerge or that may be challenging to synthesize, as in the case of the PCAs reported in Artemisia species including SCOPA.

This review of SCOPA’s ethnopharmacology, bioactivities, and constituent compounds reveals a remarkable range of traditional uses and experimental data and provides a valuable example of both the potential and the difficulties of studying complex botanical extracts. Indeed, we have described promising in vivo and in vitro data supporting SCOPA’s use for many pathologies, in particular hepatic diseases and obesity-related metabolic dysfunction, as well as proven effects of individual compounds found in SCOPA. Figure 1 illustrates the principal findings related to SCOPA. We have also presented seemingly contradictory data regarding the adipogenic effects of SCOPA, with studies showing both pro- (48, 49, 556, 557) and anti- (53, 54, 63) adipogenic activities. However, analysis of the pro-adipogenic extract and fractions revealed the presence of PCAs, known to promote adipogenesis, while these compounds were not reported in extracts that inhibited adipogenesis.

To be sure, investigation of botanical extracts is a challenging endeavor due to the enormous complexity of the mixtures, the considerable variability in extract composition from different plants of the same species (36, 46, 568, 569), the potential for unpredictable experimental artifacts (570), the imperfect methods for detecting constituent compounds, and the biased nature of investigations based on the research interests and priorities of different investigators. However, increasingly sophisticated preparatory, analytical, and computational methods are helping to overcome these difficulties. In order to enhance the reliability and translatability of natural products research, the National Center for Complementary and Integrative Health (NCCIH) has spearheaded the development of comprehensive good practices for pre-clinical investigation of natural products (567). We fully support these principles and encourage further study of the bioactivities of Artemisia scoparia, particularly in metabolism research, in accordance with these guidelines.

AUTHOR CONTRIBUTIONS

A.B. wrote the first draft of the manuscript and prepared the information for the tables. I.H wrote a small part of the review and edited the entire document. AR edited the document and prepared the final version of the Tables and Figure. JS worked with AB on original outline of the review and edited each draft. All authors contributed to the article and approved the submitted version.

FUNDING

This publication was supported by the National Center for Complementary & Integrative Health and the Office of Dietary Supplements of the National Institutes of Health (NIH) under Award Number P50AT002776 which funds the Botanical Dietary Supplements Research Center of Pennington Biomedical Research Center and the Department of Plant Biology and Pathology in the School of Environmental and Biological Sciences (SEBS) of Rutgers University.
REFERENCES

1. Bora KS, Sharma A. The Genus Artemisia: A Comprehensive Review. Pharm Biol (2011) 49:101–9. doi: 10.3109/13880290.2010.497815
2. Bish D, Kumar D, Kumar D, Dua K, Chellappan DK. Phytochemistry and Pharmacological Activity of the Genus Artemisia. Arch Pharm Res (2021) 1:3. doi: 10.1007/s12272-021-01328-4
3. Tu Y. Artemisinin—A Gift From Traditional Chinese Medicine to the World (Nobel Lecture). Angew Chem Int Ed (2016) 55:10210–26. doi: 10.1002/anie.201601967
4. Tan RX, Zheng WF, Tang HQ. Biologically Active Substances From the Genus Artemisia. Planta Med (1998) 64:295–302. doi: 10.1055/s-2006-957438
5. Abad MJ, Bedoya LM, Apaza I, Bermejo P. The Artemisia L. Genus: A Review of Bioactive Essential Oils. Molcules (2012) 17:2542–66. doi: 10.3390/molecules17032542
6. Abad Martinez MJ, Del Olmo LMB, Ticona LA, Renito PB. The Artemisia L. Genus: A Review of Bioactive Sesquiterpene Lactones. In: Studies in Natural Products Chemistry. Amsterdam, Netherlands: Elsevier BV. (2012) 37 p. 43–65. doi: 10.1016/B978-0-44-495914-0.00002-X
7. Youssif RSA. Medicinal and Non-Medicinal Uses of Some Plants Found in the Middle Region of Saudi Arabia. J Med Plant Res (2013) 7:2501–13. doi: 10.5897/JMPR12.798
8. Parveen, Upadhyay B, Roy S, Kumar A. Traditional Uses of Medicinal Plants Among the Rural Communities of Churup District in the Thar Desert, India. J Ethnopharmacol (2007) 113:38–49. doi: 10.1016/j.jep.2007.06.010
9. Sher H, Bussmann RW, Hart R, De Boer HJ. Traditional Use of Medicinal Plants Among Kalasha, Ismaili and Sunni Groups in Chitral District, Khyber Pakhtunkhwa Province, Pakistan. J Ethnopharmacol (2016) 188:57–69. doi: 10.1016/j.jep.2016.04.059
10. Hussain W, Badshah L, Ullah M, Ali M, Ali A, Hussain F. Quantitative Study of Medicinal Plants Used by the Communities Residing in Koh-E-Safaid Range, Northern Pakistani-Afghan Borders. J Ethnobot Ethnomed (2018) 14:30. doi: 10.1186/s12272-018-0229-9
11. Bhat JA, Kumar M, Bussmann RW. Ecological Status and Traditional Knowledge of Medicinal Plants in Kedar Nath Wildlife Sanctuary of Garwhal Himalaya, India. J Ethnobot Ethnomed (2013) 3:9–11. doi: 10.1186/1746-4269-9-1
12. Barkatullah, Ibrar M, Rafi A, Ben Hadda T, Mubarak MS, Patel S. Quantitative Ethnobotanical Survey of Medicinal Flora Thriving in Malakand Pass Hills, Khyber Pakhtunkhwa, Pakistan. J Ethnopharmacol (2015) 169:335–46. doi: 10.1016/j.jep.2015.04.052
13. Mahmood A, Mahmood A, Naseem Malik R, Khan Shinwari Z. Indigenous Knowledge of Medicinal Plants From Gujranwala District, Pakistan. J Ethnopharmacol (2013) 148:714–23. doi: 10.1016/j.jep.2013.05.035
14. Khan M, Kumar S, Hamal IA. Medicinal Plants of Sewa River Catchment Area in the Northwest Himalaya and Its Implication for Conservation. Ethnobot Leaf (2009) 13:1113–52.
15. Au DT, He Q, Cheng YY, Xiao PG. Ethnobotany of Medicinal Plants From Tian Mu Shan Biosphere Reserve, Zhejiang-Provence, China. Asian J Plant Sci (2006) 5:46–53. doi: 10.3923/aps.2006.46.653
16. Wright M, Watson MF. Tibetan Medicinal Plants. In: C Kletter and M Kriechbaum, editors. vol. 383. Stuttgart: Medpharm Scientific Publishers (2001) p. 77. Edinburgh J Bot (2002). doi: 10.1016/s09640280(02)60291
17. Safa O, Soltanipoor MA, Rastegar S, Kazemi M, Nourbakhsh Dehkordi K, Ghannadi A. An Ethnobotanical Survey on Hormozgan Province, Iran. Avicenna J Phytomed (2013) 3:57–61. doi: 10.5897/Ajp.2012.12
18. Hayat M, Hayat MQ, Khan MA, Ashraf M, Jabeen S. Ethnobotany of the Genus Artemisia L. (Asteraceae) in Pakistan. Ethnobot Res Appl (2009) 7:147–62. doi: 10.17348/era.7.0.147-162
19. Ishtiaq M, Masroo M, Ajaib M, Ahmed M, Hussain I, Khanam H, et al. Ethnopharmacological and Folklore Inventory of Wild Plants Used by Rural Communities of Valley Samahni, District Bhimber Azad Jammu and Kashmir, Pakistan. PloS One (2021) 16(1):e2433151. doi: 10.1371/journal.pone.02433151
20. Hussain W, Ullah M, Dastagir G, Badshah L. Quantitative Ethnobotanical Appraisal of Medicinal Plants Used by Inhabitants of Lower Kurram, Khyber Agency, Pakistan. J Ethnopharmacol (2018) 8:313–29.
21. Naved M, Hejazi Y, Abbas M, Kamboh AA, Khan GJ, Shumzaid M, et al. Chlorogenic Acid (CGA): A Pharmacological Review and Call for Further Research. BioMed Pharmacother (2018) 97:67–74. doi: 10.1016/j.biopha.2017.10.064
22. Khan SW, Bot PJ, Wali Khan And S, Khatsoon S. Ethnobotanical Studies on Some Useful Herbs of Haramosh and Burgote Valleys in Gilgit, Northern Areas of Pakistan. Pakistan J Bot (2008) 40:43–58.
23. Joshi R, Satyal P, Setzer W. Himalayan Aromatic Medicinal Plants: A Review of Their Ethnopharmacology, Voltatile Phytochemistry, and Biological Activities. Medicines (2016) 3:6. doi: 10.3390/medicines3010006
24. Abbas Z, Khan SM, Alam J, Khan SW, Abbas AM. Medicinal Plants Used by Inhabitants of the Shigar Valley, Baltistan Region of Karakorum Range-Pakistan. J Ethnobot Ethnomed (2017) 13:53. doi: 10.1186/s12272-017-0172-9
25. Ganie AH, Tali BA, Shapoo GA, Nawchoo IA, Khuroo AA. Ethno-Survey of Traditional Use of Plants as Aphrodisiacs in Kashmir Himalaya, India. J Herb Med (2019) 17–18:100256. doi: 10.1016/j.jhermed.2019.100256
26. Rana CS, Sharma A, Kumar N, Dangwal LR, Tiwari JK. Ethnopharmacology of Some Important Medicinal Plants of Nanda Devi National Park (NDNP) Uttarakhand, India. Nat Sci (2010) 8:9–14.
27. China Medical Science Press. Pharmacopoeia of the People's Republic of China. 10th Ed. Beijing, China: China Medical Science Press (2017).
28. Cai Y, Zheng Q, Sun R, Wu J, Li X, Liu R. Recent Progress in the Study of Artemesia Scoparia Herbs (Yin Chen), a Promising Medicinal Herb for Liver Diseases. BioMed Pharmacother (2020) 130:110513. doi: 10.1016/j.biopharma.2020.110513
29. Youssif A. Medicinal and Non-Medicinal Uses of Some Plants Found in the Middle Region of Saudi Arabia. J Med Plant Res (2013) 7:2501–17. doi: 10.5897/JMPR12.798
30. Yeung H. Handbook of Chinese Herbal Formulas. 2nd Ed. Rosemead, CA: Institute of Chinese Medicine (1995).
31. Nadeem M, Khan Shinwari Z, Quaiser M. Screening of Folk Remedies by Genus Artemisia Based on Ethnomedicinal Surveys and Traditional Knowledge of Native Communities of Pakistan. Pak J Bot (2013) 45:111–7.
32. Khan SW, Bot PJ, Wali Khan And S, Khatsoon S. Ethnobotanical Studies on Some Useful Herbs of Haramosh and Bugrote Valleys in Gilgit. Northern Areas Pakistan (2008) 40:43–58.
33. Ding J, Wang L, He C, Zhao J, Si L, Huang H. Artemisia Scoparia: Traditional Uses, Active Constituents and Pharmacological Effects. J Ethnopharmacol (2021) 273:113960. doi: 10.1016/j.jep.2021.113960
34. Duah Boakye Y, Shaheen S, Nawaz H, Nisar S, Azem MW. Artemisia Scoparia: A Review on Traditional Uses, Phytochemistry and Pharmacological Properties. IJCRS (2017) 12:92–7.
120. Zutshi U, Rao PG, Soni A, Atal CK. Absorption, Distribution and Excretion of Scoparone: A Potent Hypotensive Agent. Indian J Exp Biol (1978) 16:638–8.

121. Houlé JRS, Payá M. Pharmacological and Biochemical Actions of Simple Coumarins: Natural Products With Therapeutic Potential. Gen Pharmacol (1996) 27:713–22. doi: 10.1016/0306-3623(95)02112-4

122. Huang HC, Lee CR, Weng YI, Lee MC, Lee YT. Vasodilator Effect of Scoparone (6,7-Dimethoxycoumarin) From a Chinese Herb. Eur J Pharmacol (1992) 218:123–8. doi: 10.1016/0928-4859(92)90155-W

123. Yamahara J, Kobayashi G, Matsuda H, Katayama T, Fujimura H. Vascular Dilatory Action of the Chinese Crude Drug. II. Effects of Scoparone on Calcium Mobilization. Chem Pharm Bull (1989) 37:485–9. doi: 10.1248/cpb.37.485

124. Yamahara J, Kobayashi G, Matsuda H, Katayama T, Fujimura H. The Effect of Scoparone, a Coumarin Derivative Isolated From the Chinese Crude Drug Artemisiae Capillaris Flos, on the Heart. Chem Pharm Bull (1989) 37:1297–9. doi: 10.1248/cpb.37.1297

125. Yamahara J, Kobayashi G, Matsuda H, Katayama T, Fujimura H. Vascular Dilatory Action of the Chinese Crude Drug. III. Effects of Scoparone From Chestnut Inner Shell on Platelet-Dependent Growth Factor-BB-Induced Vascular Smooth Muscle Cell Migration and Vascular Neointima Hyperplasia. J Sci Food Agric (1995) 69:1297–308. doi: 10.1002/jsfa.9674

126. Cho DY, Ko HM, Kim J, Kim BW, Yun YS, Park JI, et al. Scoparone Inhibits Tetrachloride-Induced Hepatic Injury by Antioxidative Activities in Rats. Exp Toxicol Pathol (2011) 63:325–30. doi: 10.1016/j.etp.2010.02.006

127. Hoult JRS, Paya M. Pharmacological and Biochemical Actions of Simple Coumarins: Natural Products With Therapeutic Potential. Gen Pharmacol (1996) 27:713–22. doi: 10.1016/0306-3623(95)02112-4

128. Liu B, Saha PK, Huang W, Chen W, Abu-Elheiga LA, Wakil SJ, et al. Activation of Nuclear Receptor CAR Ameliorates Diabetes and Fatty Liver Disease. Proc Natl Acad Sci USA (2009) 106:18831–6. doi: 10.1073/pnas.0909731106

129. Gao J, He J, Zhai Y, Wada T, Xie W. The Constitutive Androstane Receptor Is an Antigen-Dependent Nuclear Receptor That Improves in Sulin Sensitivity. J Biol Chem (2009) 284:25984–92. doi: 10.1074/jbc.M109.016808

130. Dong B, Saha PK, Huang W, Chen W, Abu-Elheiga LA, Wakil SJ, et al. Activation of Nuclear Receptor CAR Ameliorates Diabetes and Fatty Liver Disease. Proc Natl Acad Sci USA (2009) 106:18831–6. doi: 10.1073/pnas.0909731106

131. Jiang M, Xie W. Role of the Constitutive Androstane Receptor in Obesity and Type 2 Diabetes: A Case Study of the Endobionic Function of a Xenobiotic Receptor. Drug Metab Rev (2013) 45:135–6. doi: 10.1016/j.dmr.2013.0602532. 2012.743561

132. Li X, Wang Z, Klaunig JE. Modulation of Xenobiotic Nuclear Receptors in High-Fat Diet Induced Non-Alcoholic Fatty Liver Disease. Toxicology (2018) 410:199–213. doi: 10.1016/j.tox.2018.08.007

133. Jiang SH, Hsieh MT, Hsu JL, Liu HK, Liang FP, et al. Studies of Coumarin Derivatives for Constitutive Androstane Receptor (CAR) Activation. Molecules (2020) 26(1):164. doi: 10.3390/molecules26010164

134. Jung SI, Kim Y-J, Lee W-Y, Kwak KC, Baek H, Beum Kwak G, et al. Scoparone From Artemisia Capillaris Inhibits the Release of Inflammatory Mediators in RAW 264.7 Cells Upon Stimulation Cells by Interferon-γ Plus LPS. Arch Pharm Res (2005) 28:203–8. doi: 10.1002/arp.2077

135. Noh JR, Kim YH, Gang GT, Hwang JH, Lee HS, Ly SY, et al. Antioxidant Effects of the Chestnut (Castanea Crenata) Inner Shell Extract in T-BHP-Induced Myocardial Injury. [Korean] Molecules (2020) 25:3136–8. doi: 10.3390/molecules250103136

136. Xia J, Li CY, Wang H, Zhang QM, Han ZM. Therapeutic Effects of Scoparone on Platelet-Derived Growth Factor-β1-Induced Myocardial Injury. [Korean] J Biol Chem (2009) 284:25984–92. doi: 10.1074/jbc.M109.016808

137. Noh JR, Kim YH, Gang GT, Hwang JH, Lee HS, Ly SY, et al. Antioxidant and Intestinal Anti-Inflammatory Effects of Plant-Derived Coumarin Derivatives. Phytotherapy (2014) 21:20–6. doi: 10.1016/j.phymed.2013.09.001

138. Xia J, Li CY, Wang H, Zhang QM, Han ZM. Therapeutic Effects of Scoparone on Platelet-Derived Growth Factor-β1-Induced Myocardial Injury. [Korean] J Biol Chem (2009) 284:25984–92. doi: 10.1074/jbc.M109.016808

139. Noh JR, Kim YH, Gang GT, Hwang JH, Lee HS, Ly SY, et al. Hepatoprotective Effects of Chestnut (Castanea Crenata) Inner Shell Extract Against Chronic Ethanol-Induced Oxidative Stress in C57BL/6 Mice. Food Chem Toxicol (2010) 48:3177–83. doi: 10.1016/j.fct.2010.08.018

140. Noh JR, Kim YH, Gang GT, Hwang JH, Lee HS, Ly SY, et al. Hepatoprotective Effects of Chestnut (Castanea Crenata) Inner Shell Extract Against Chronic Ethanol-Induced Oxidative Stress in C57BL/6 Mice. Food Chem Toxicol (2010) 48:3177–83. doi: 10.1016/j.fct.2010.08.018

141. Sourivong P, Schronerová K, Babincová M. Scoparone Inhibits Ultraviolet Radiation-Induced Lipid Peroxidation. Z Nar Notarosch - Sect C J Biassi (2007) 62:61–4. doi: 10.1515/sm-2007-1-211

142. Noh JR, Gang GT, Kim YH, Yang KJ, Hwang JH, Lee HS, et al. Antioxidant Effects of the Chestnut (Castanea Crenata) Inner Shell Extract in T-BHP-Treated HepG2 Cells, and CCL4- and High-Fat Diet-Treated Mice. Food Chem Toxicol (2010) 48:3177–83. doi: 10.1016/j.fct.2010.08.018

143. Noh JR, Kim YH, Gang GT, Hwang JH, Lee HS, Ly SY, et al. Hepatoprotective Effects of Chestnut (Castanea Crenata) Inner Shell Extract Against Chronic Ethanol-Induced Oxidative Stress in C57BL/6 Mice. Food Chem Toxicol (2011) 49:1537–43. doi: 10.1016/j.fct.2011.03.045

144. Liu S, Zhou SW. 6,7-Dimethoxycoumarin Attenuated Cisplatin-Induced DNA Interstrand Crosslink and DNA-Protein Crosslink in Primary Cultured Rabbit Kidney Proximal Tubular Cells. Acta Pharm Sin (2009) 20:391–4

145. Xu M, Cai J, Wei H, Zhou M, Xu P, Huang H, et al. Scoparone Protects Against Pancreatic Fibrosis via TGF-ß/Smad Signaling in Rats. Cell Physiol Biochem (2016) 40:277–86. doi: 10.1159/000452544
Gao Y, Xi B, Li J, Li Z, Xu J, Zhong M, et al. Scoparone Alleviates Hepatic Fibrosis by Inhibiting the TLR-4/NF-κB Pathway. J Cell Physiol (2021) 236:3044–58. doi: 10.1002/jcp.30083

Ivanovska N, Yossifova T, Vassileva E, Kostova I. Effect of Some Hydroxycoumarins on Complement-Mediated Hemolysis in Human Serum. Methods Find Exp Clin Pharmacol (1994) 16:557–62.

Lu C, Li Y, Hu S, Cai Y, Yang Z, Peng K. Scoparone Prevents IL-1ß-Induced Inflammatory Response in Human Osteoarthritic Chondrocytes Through the PI3K/Akt/NF-κB Pathway. BioMed Pharmacother (2018) 106:1169–74. doi: 10.1016/j.biopha.2018.07.062

Choi BR, Kim HK, Park JK. Penile Erection Induced by Scoparone From Artemisia Capillaris Through the Nitric Oxide-Cyclic Guanosine Monophosphate Signaling Pathway. World J Mens Health (2017) 35:196. doi: 10.1053/j.wmhm.170218

Yang JY, Koo JH, Song YG, Kwon KB, Lee JH, Sohn HS, et al. Stimulation of Melanogenesis by Scoparone in B16 Melanoma Cells. Acta Pharmacol Sin (2006) 27:1467–73. doi: 10.1111/j.1745-7254.2006.00435.x

Lee SH, Lee JY, Kwon YJ, Jang HD. Anti-Osteoarticular Activity of Artemisia Capillaris Thumb. Extract Depends Upon Attenuation of Osteoclast Differentiation and Bone Resorption-Associated Acidification Due to Chlorogenic Acid, Hyperoside, and Scoparone. Int J Mol Sci (2017) 18 (2):322. doi: 10.3390/ijms18020322

Jung HA, Park JJ, Islam MN, Jin SE, Min BS, Lee J-H, et al. Inhibitory Activity of Coumarins From Artemisia Capillaris Against Advanced Glycation Endproduct Formation. Arch Pharm Res (2012) 35:1021–35. doi: 10.1007/s12272-012-0610-0

Lee HI, Lee MK. Coordinated Regulation of Scopoletin at Adipose Tissue-Liver Axis Improved Alcohol-Induced Lipid Dysmetabolism and Inflammation in Rats. Toxicol Lett (2015) 237:210–8. doi: 10.1016/j.toxlet.2015.06.016

Choi JY, Cho HW, Choi MS, Park SK, et al. Scopoletin Supplementation Ameliorates Steatosis and Inflammation in Diabetic Mice. Phyther Res (2017) 31:1795–804. doi: 10.1002/tr.5925

Chung WC, Wu SC, Xu KD, Liao BC, Wu JF, Cheng AS. Scoparone Protects Against Methyglyoxal-Induced Hyperglycemia and Insulin Resistance Mediated by Suppression of Advanced Glycation Endproducts (AGEs) Generation and Anti-Glycation. Molecules (2015) 20:7286–801. doi: 10.3390/molecules20022786

Kalpana K, Priyadarshini E, Sreeja S, Jagan K, Anuradha CV. Scopoletin Intervention in Pancreatic Endoplasmic Reticulum Stress Induced by Lipotoxicity. Cell Stress Chaperones (2018) 23:857–69. doi: 10.1007/s12192-018-0893-2

Kalpana K, Sathiya Priya C, Dipti N, Vidhya R, Anuradha CV. Scopoletin Supplementation of Scopoletin Improves Insulin Sensitivity by Attenuating the Derangements of Insulin Signaling Through AMPK. Mol Cell Biochem (2019) 453:65–78. doi: 10.1007/s11010-018-3432-7

Jang JH, Park JE, Han JS. Scopoletin Inhibits t-Glucosidase In Vitro and Alleviates Postprandial Hyperglycemia in Mice With Diabetes. Eur J Pharmacol (2018) 834:152–6. doi: 10.1016/j.ejphar.2018.07.032

Zhang WY, Lee JJ, Kim Y, Kim IS, Park JS, Myung CS. Amelioration of Insulin Resistance by Scoparone in High-Glucose-Induced, Insulin-Resistant HepG2 Cells. Hnorn Metab Res (2010) 42:930–5. doi: 10.1055/s-0030-1265219

Kim J, Kim CS, Lee YM, Sohn E, Jo K, Shin SD, et al. Scopoletin Inhibits Rat Aldose Reductase Activity and Cataractogenesis in Galactose-Fed Rats. Evidence-Based Complement Altern Med (2013) 2013:78138. doi: 10.1155/2013/78138

Lee J, Kim NH, Nam JW, Lee YM, Jang DS, Kim YS, et al. Scopoletin From the Flowers of Magnolia Fargesii Inhibits Protein Glycation, Aldose Reductase, and Cataractogenesis Ex Vivo. Arch Pharm Res (2010) 33:1317–23. doi: 10.1007/s12272-010-0994-z

Ojewole JAO, Adesina SK. Cardiovascular and Neuromuscular Actions of Scopoletin From Fruit of Tetrapleurae Tetrapetra. Planta Med (1983) 49:99–102. doi: 10.1055/s-0030-1265219

Lagunas-Herrera H, Tortoriello J, Herrera-Ruiz M, Martinez-Henández GB, Zamilpa A, Santamaria LA, et al. Acute and Chronic Antihypertensive Effect of Fractones, Tilisroide and Scopoletin From Malva Parviflora. Biol Pharm Bull (2019) 42:218–25. doi: 10.1248/bpb.b18-00355

Ojewole JAO, Adesina SK. Mechanism of the Hypotensive Effect of Scopoletin Isolated From the Fruit of Tetrapleurae Tetrapetra. Planta Med (1983) 49:46–50. doi: 10.1055/s-1983-529899

Thuong PT, Na M, Seong RS, Lee YM, Sok DE, et al. Inhibitory Effect of Coumarins From Weigela Subsessilis on Low Density Lipoprotein Oxidation. Biol Pharm Bull (2005) 28:1095–7. doi: 10.1248/bpb.28.1095
Inhibitory Coumarinaries on Cholangiocarcinoma Cells. *Integr Cancer Ther* (2019) 18:15347351418200444. doi: 10.1177/15347351418200444

214. Deng S, Pala AK, Wei J, Su CX, Zhou BN, Jensen JC. Lipoxigenase Inhibitory Constituents of the Fruits of Noni (Morinda Citifolia) Ligated in Tehran. *J Nat Prod* (2007) 70:859–62. doi: 10.1021/np0605539

215. Pan R, Gao XH, Li Y, Xiao YF, Dai Y. Anti-Arthritic Effect of Scopoletin, a Coumarin Compound Occurring in Erycbe obsfusiola Benth Stems, Is Associated With Decreased Angiogenesis in Synovium. *Fundam Clin Pharmacol* (2010) 24:747–90. doi: 10.1111/j.1472-822X.2009.00784.x

216. Shaw CY, Chen CH, Hsu CC, Chen CC, Tsai YC. Antioxidant Properties of Scopoletin Isolated From Sinomonomium Acutum. *Phyther Res* (2003) 17:823–5. doi: 10.1002/pr.1138

217. Kim AR, Zou YN, Park TH, Shim KH, Kim MS, Kim ND, et al. Active Components From Artemisia Iwagymi Displaying ONOO– Scavenging Activity. *Phyther Res* (2004) 18:1–7. doi: 10.1002/pr.1358

218. Abreu PM, Matthew S, Gonzalez T, Vanickoiva L, Costa D, Gomes A, et al. Isolation and Identification of Antioxidants From Pedilanthus Tithymaloideis. *J Nat Med* (2008) 62:67–70. doi: 10.1007/s11148-007-0186-z

219. Khan S, Riaz N, Afza N, Malik A, Aziz-Ur-Rehmana, Iqbal L, et al. Antioxidant Constituents From Cotononeaster Racemifora. *J Asian Nat Prod Res* (2009) 11:44–8. doi: 10.1080/1472-8206.2009.1057347545

220. Kassim NK, Rahman M, Ismail A, Sukari MA, Ee GCL, Nasir NM, et al. Antioxidant Activity-Guided Separation of Coumarins and Lignan From Melicope Glabra (Rubaceae). *Food Chem* (2013) 139:87–92. doi: 10.1016/j.foodchem.2013.01.108

221. Kassim NK, Rahman M, Ismail A, Sukari MA, Ee GCL, Nasir NM, et al. Antioxidant Activity-Guided Separation of Coumarins and Lignan From Melicope Glabra (Rubaceae). *Food Chem* (2013) 139:87–92. doi: 10.1016/j.foodchem.2013.01.108

222. Nugroho A, Lim SC, Karki S, Choi JS, Park HJ. Simultaneous Quantification and Validation of New Peroxynitrite Scavengers From Artemisia Iwagymoi. *Pharm Biol* (2015) 53:653–61. doi: 10.3109/13888209.2014.936022

223. Parra C, Soto E, León G, Salas CO, Heinrich M, echibúri-Chau C. Nutritional Composition, Antioxidant Activity and Isolation of Scopoletin From Senecon Nutans: Support of Ancestral and New Uses. *Nat Prod Res* (2018) 32:719–22. doi: 10.1080/1748617X.2017.1335726

224. Panda S, Kar A. Evaluation of the Antithyroid, Antioxidative and Antihyperglycemic Activity of Scopoletin From Aegle Marmelos Leaves in Hyperthyroid Rats. *Phyther Res* (2006) 20:1103–5. doi: 10.1002/pr.2014

225. Ng TB, Liu F, Lu Y, Cheng CHK, Wang Z. Antioxidant Activity of Compounds From the Medicinal Herb Aster Tataricus. *Comp Biochem Physiol - C Toxicol Pharmacol* (2003) 136:109–15. doi: 10.1016/S1532-0456 (03)00170-4

226. Toda S. Inhibitory Effects of Phenylpropanoid Metabolites on Copper-Induced Protein Oxidative Modulation of Mouse Brain Hypothalamus In Vitro. *Biol Trace Elem Res* (2004) 28:205–31. doi: 10.1385/BTER:28:2:205

227. Pradhan P, Majhi O, Biswas A, Joshi VK, Sinha D. Enhanced Accumulation of Reduced Gluthione by Scopoletin Improves Survivability of Dopaminergic Neurons in Parkinson’s Model. *Cell Death Dis* (2020) 11:1–11. doi: 10.1038/s41419-020-02942-8

228. Silvan AM, Abd MJ, Bermejo P, Sollihuer M, Villar A. Antiinflammatory Activity of Coumarinaries From Santolina Olibongolia. *J Nat Prod* (1996) 59:1183–5. doi: 10.1021/np600422f

229. Silvan AM, Abd MJ, Bermejo P, Villar A. Effects of Compounds Extracted From Santolina Olibongolia On TXB2 Release in Human Platelets. *Inflammapharmacology* (1998) 6:255–63. doi: 10.1007/10767-998-0024-2

230. Kang TH, Pae HO, Jeong SJ, Yoo JC, Choi RM, Jun CD, et al. Scopoletin: An Inducible Nitric Oxide Synthesis Inhibitory Active Constituent From Artemisia Feddei. *Planta Med* (1999) 65:400–3. doi: 10.1055/s-1999-14014

231. Kim HJ, Jang S, Kim YJ, Chung HT, Yun YG, Kang TH, et al. Scopoletin Suppresses Pro-Inflammatory Cytokines and PGE2 From LPS-Stimulated Cell Line, RAW 264.7 Cells. *PloS One* (2006) 7:456–8. doi: 10.1038/s41419-020-02942-8

232. Moon PD, Lee BH, Jeong HJ, An HJ, Park SJ, Kim HR, et al. Use of Scopoletin to Inhibit the Production of Inflammatory Cytokines Through
Inhibition of the k/b-NF-xB Signal Cascade in the Human Mast Cell Line
HMC-1. Eur J Pharmacol (2007) 555:218–25. doi: 10.1016/j.ejphar.2006.10.021

234. Choi YG, Yeo S, Kim SH, Lim S. Anti-Inflammatory Changes of Gene
Expression by Artemisia Iwayomogi in the LPS-Stimulated Human Gingival
Fibroblast: Microarray Analysis. Arch Pharm Res (2012) 35:549–63. doi:
10.1007/s12277-012-0319-0

235. Dou Y, Tong B, Wei Z, Li Y, Xia Y, Dai Y. Scopoletin Suppresses IL-6
Production From Fibroblast-Like Synoviocytes of Adjuvant Arthritis Rats
Induced by IL-1β Stimulation. Int Immunopharmacol (2013) 17:1037–43. doi:
10.1016/j.intimp.2013.10.011

236. Kamino T, Shimokura T, Morita Y, Tezuka Y, Nishizawa M, Tanaka K.
Muschietti L, Gorzalczany S, Ferraro G, Acevedo C, Martino V. Phenolic
Sakthivel KM, Vishnupriya S, Priya Dharshini LC, Rasmi RR, Ramesh B.
238. Pereira dos Santos Nascimento MV, Arruda-Silva F, Gobbo Luz AB, Baratto
Farah MH, Samuelsson G. Pharmacologically Active Phenylpropanoids
239. Ribas CM, Meotti FC, Nascimento FP, Jacques AV, Dafre AL, Rodrigues
240. Capra JC, Cunha MP, Machado DG, Zomkowski ADE, Mendes BG, Santos

242. Mishcetti L, Gorzalczany S, Ferraro G, Acevedo C, Martino V. Phenolic
Compounds With Anti-Inflammatory Activity From Eupatorium
Bunifolium. Planta Med (2001) 67:745–4. doi: 10.1055/s-2001-18355

243. Farah MH, Samuelsson G. Pharmacologically Active Phenylpropanoids
From Convolvulus Pluricaulis on Reflux Esophagitis and Gastric Ulcer in Rats.
EjPharmacol (2011) 134:243–50. doi: 10.1016/j.ejph.2012.12.004

244. Ying Z, Dai Y, Hao H, Pan R, Yao X, Wang Z. Anti-Inflammatory Effects of
Scopoletin and Underlying Mechanisms. Int Immunopharmacol (2012) 14:454–62. doi:
10.1016/j.intimp.2012.07.024

245. Sakhthivel KM, Vishnupriya S, Priya Dharsimi LC, Rasmi RR, Ramesh B. Modulation of Multiple Cellular Signalling Pathways as Targets for Anti-
Inflammatory and Anti-Tumorigenesis Action of Scopoletin. J Pharm Pharmacol (2013) 1:13:rgab047. doi: 10.1093/jpp/rgab047

246. Mahattanadul S, Radhitid W, Nima S, Phoongombut N, Ratasanuvon P, Kasiwong S. Effects of Morinda Citrifolia Aqueous Fruit Extract and Its
Biosynthetic Scopoletin on Reflux Esophagitis and Gastric Ulcer in Rats.
EjPharmacol (2011) 134:243–50. doi: 10.1016/j.ejph.2012.12.004

247. Zhang F, Zhang Y, Yang T, Ye QZ, Tian J, Fang HR, et al. Scopoletin Suppresses Activation of Dendritic Cells and Pathogenesis of Experimental
Autoimmune Encephalomyelitis by Inhibiting NF-xB Signaling. Front Pharmacol (2019) 10:863. doi: 10.3389/fphar.2019.00863

248. Loo L, Sun T, Yang L, Liu A, Liu QQ, Tian QQ, et al. Scopoletin Ameliorates Anxiety-Like Behaviors in Complete Freund’s Adjuvant-Induced Mouse
Model. Mol Brain (2020) 13:1–13. doi: 10.1186/s13041-020-0560-2

249. Zhang W, Zhao W, Ge C, Li X, Sun Z. Scopoletin Attenuates Intracerebral
Hemorrhage-Induced Brain Injury and Improves Neurological Performance
in Rats. Neuroinflammationmodul (2021) 28:74–81. doi: 10.1159/000507531

250. Lee JH, Ki TL, Jae HY, Nam IB, Dae KK. Acetylcholinesterase Inhibitors From
the Twigs of Vaccinium Oldhami Miquel. Arch Pharm Res (2004) 27:53–6. doi: 10.1007/BF02989046

251. Orhan I, Tosun F, Şener B, Courman, Anthroquinone and Stilbene
Derivatives With Anticholinesterase Activity. J For Naturforsch - Sect C J Biosci (2008) 63:366–70. doi: 10.1515/znc-2008-5-610

252. Suchai N, Kanokmedhakul S, Kanokmedhakul K, Moosophon P, Boonyarat C, Plekrateko E, et al. Phytochemical and Pharmacological
Analysis of Scopoletin Extract from Scopoliaceae Scopoliaceae
4. Antioxidant Potential of Scopoletin Isolated From Canarium Patentinervium
Miq. (Burseraceae Kunth).

253. Malik J, Karan M, Vaisith K. Attenuating Effect of Bioactive Coumarins From Convolvulus Pluricaulis on Scopolamine-Induced Amnesia in Mice. Nat Prod Res (2016) 30:578–82. doi: 10.1080/17435349.2015.1025398

254. Hornick A, Lieb A, Vo NP, Rollinger JM, Stupper H, Prat H. The Scopoletin Potententiates Acetylcholine Release From
Synaptosomes, Amplifies Hippocampal Long-Term Potentiation and Amelioration Anticholinergic- and Age-Impaired Memory. Neuroscience (2011) 197:280–92. doi: 10.1016/j.neuroscience.2011.09.006

255. Maneef-Esfahani HR, Amini M, Goodarzi N, Saidmohammadi F, Hajiaghaee R, Faramarzi MA, et al. Coumarin Compounds of
Biebersteinia Multifida Roots Show Potential Antioxidant Efects in Mice. DARU J Pharm Sci (2013) 21:51. doi: 10.1186/2008-2231-21-51

256. Pandy V, Vijeepallam K. Antipsychotic-Like Activity of Scopoletin and Rutin Against the Positive Symptoms of Schizophrenia in Mice Models. Exp
Anim (2017) 66:417–23. doi: 10.1538/expanim.17-0030

257. Mishra N, Oraon A, Dev A, Jayaprakash V, Basu A, Pattnaik AK, et al. Anticonvulsant Activity of Benkara Malabarica (Linn.) Root Extract: In vitro
and in vivo Investigation. J Ethnopharmacol (2010) 128:533–6. doi: 10.1016/
j.jep.2010.01.042

258. Zhou R, Kan S, Cai S, Sun R, Yuan H, Yu B. Scopoletin Activates Adenosine Monophosphate-Activated Protein Kinase/Mammalian Target of
Rapamycin Signaling Pathway and Improves Functional Recovery After
Spinal Cord Injury in Rats. Pharmacology (2020) 105:349–59. doi: 10.1159/
000503866
Tissues of Experimental Diabetic Rats. Biochimie (2013) 95:366–73. doi: 10.1016/j.bioch.2012.10.008

306. Choi RV, Ham JR, Lee MK. Esculetin Prevents Non-Alcoholic Fatty Liver in Diabetic Mice Fed High-Fat Diet. Chem Biol Interact (2016) 260:13–21. doi: 10.1016/j.cbi.2016.10.013

307. Kim Y, Park Y, Namkoong S, Lee J. Esculetin Inhibits the Inflammatory Response by Inducing Heme Oxygenase-1 in Cocultured Macrophages and Adipocytes. Food Funct (2014) 5:2371–7. doi: 10.1039/c4fo00351a

308. Pan H, Wang BH, Lv W, Jiang Y, He L. Esculetin Induces Apoptosis in Human Gastric Cancer Cells Through a Cyclophilin D-Mediated Mitochondrial Permeability Transition Pore Associated With ROS. Cell Mol Biol (2015) 260:13–21. doi: 10.1016/j.cbi.2015.09.015

309. Park C, Jin CY, Kim KY, Choi IW, Kwon TK, Choi RT, et al. Induction of Apoptosis by Esculetin in Human Leukemia U937 Cells Through Activation of JNK and ERK. Toxicol Appl Pharmacol (2008) 227:219–28. doi: 10.1016/j.taap.2007.10.003

310. Pan SL, Huang YW, Gub JH, Chang YL, Peng CY, Teng CM. Esculetin Inhibits Ras-Mediated Cell Proliferation and Attenuates Vascular Restenosis Following Angioplasty in Rats. Biochem Pharmacol (2003) 65:1897–905. doi: 10.1016/S0006-2952(03)00161-8

311. Junior AG, Tolouei SEL, dos Reis L. Anti-Proliferative Effects Against Non-Small-Cell Lung Carcinoma by a Coumarin Derivative, Evokes Ca2+ Movement and Activation of PLC-δ1-PKC-AKT Activation in Human Platelets. Int J Mol Sci (2019) 20:2731. doi: 10.3390/ijms20112731

312. Abdallah H, Farag M, Osman K, Kim DH, Kang K, Pan CH, et al. Isolation of Major Phenolics From Launaea Spinosa and Their Protective Effect on HepG2 Cells Damaged With T-BHP. Pharm Biol (2016) 54:536–41. doi: 10.3109/15588490.2015.1052885

313. Tien YC, Liao JC, Chiu CS, Huang TH, Huang CY, Chang WT, et al. Esculetin Ameliorates Hepatic Fibrosis in High Fat Diet Induced Non-Alcoholic Fatty Liver Disease by Regulation of FoxO1 Mediated Pathway. Pharmacol Rep (2017) 69:666–72. doi: 10.1016/j.pharep.2017.02.005

314. Kim AD, Han X, Piao MJ, Hewage SRKM, Hyun CL, Cho SJ, et al. Esculetin Inhibits Oxidative Stress and Apoptosis in Human Leukemia U937 Cells of Experimental Diabetic Rats. Biochimie (2013) 95:781–7. doi: 10.1016/j.bioch.2013.02.012

315. Kim Y, Lee J. Esculetin Inhibits Apoptosis in Human Gastric Cancer Cells Through a Cyclophilin D-Mediated Mitochondrial Permeability Transition Pore Associated With ROS. Chem Biol Interact (2015) 242:51–60. doi: 10.1016/j.cbi.2015.09.015

316. Park C, Jin CY, Kim KY, Choi IW, Kwon TK, Choi RT, et al. Induction of Apoptosis by Esculetin in Human Leukemia U937 Cells Through Activation of JNK and ERK. Toxicol Appl Pharmacol (2008) 227:219–28. doi: 10.1016/j.taap.2007.10.003

317. He Y, Li C, Ma Q, Chen S. Esculetin Inhibits Oxidative Stress and Apoptosis in Human Leukemia U937 Cells. Biochimie (2011) 93:781–7. doi: 10.1016/j.bioch.2011.04.002

318. He Y, Li C, Ma Q, Chen S, Esculetin Inhibits Oxidative Stress and Apoptosis in HepG2 Cells: Possible Involvement of Heme Oxygenase-1. Biochem Pharmacol (2011) 83:209–16. doi: 10.1016/j.bcp.2010100830

319. Kim Y, Lee J. Esculetin Inhibits Apoptosis in Human Gastric Cancer Cells Through a Cyclophilin D-Mediated Mitochondrial Permeability Transition Pore Associated With ROS. Chem Biol Interact (2015) 242:51–60. doi: 10.1016/j.cbi.2015.09.015

320. He Y, Li C, Ma Q, Chen S. Esculetin Inhibits Oxidative Stress and Apoptosis in HepG2 Cells: Possible Involvement of Heme Oxygenase-1. Biochem Pharmacol (2011) 83:209–16. doi: 10.1016/j.bcp.2010100830

321. Kim Y, Lee J. Esculetin Inhibits Apoptosis in Human Gastric Cancer Cells Through a Cyclophilin D-Mediated Mitochondrial Permeability Transition Pore Associated With ROS. Chem Biol Interact (2015) 242:51–60. doi: 10.1016/j.cbi.2015.09.015

322. He Y, Li C, Ma Q, Chen S. Esculetin Inhibits Oxidative Stress and Apoptosis in HepG2 Cells: Possible Involvement of Heme Oxygenase-1. Biochem Pharmacol (2011) 83:209–16. doi: 10.1016/j.bcp.2010100830

323. Kim Y, Lee J. Esculetin Inhibits Apoptosis in Human Gastric Cancer Cells Through a Cyclophilin D-Mediated Mitochondrial Permeability Transition Pore Associated With ROS. Chem Biol Interact (2015) 242:51–60. doi: 10.1016/j.cbi.2015.09.015

324. Lee SY, Lim TG, Chen H, Jung SK, Lee HJ, Lee MH, et al. Esculetin Suppresses Proliferation of Human Colon Cancer Cells by Directly Targeting β-Catenin. Cancer Prev Res (2013) 6:1356–64. doi: 10.1158/1940-6275.CAPR-13-0241

325. He Y, Li C, Ma Q, Chen S. Esculetin Inhibits Oxidative Stress and Apoptosis in Human Leukemia U937 Cells of Experimental Diabetic Rats. Biochimie (2013) 95:781–7. doi: 10.1016/j.bioch.2013.04.002

326. Pan H, Wang BH, Lv W, Jiang Y, He L. Esculetin Induces Apoptosis in Human Gastric Cancer Cells Through a Cyclophilin D-Mediated Mitochondrial Permeability Transition Pore Associated With ROS. Chem Biol Interact (2015) 242:51–60. doi: 10.1016/j.cbi.2015.09.015

327. Duan J, Shi J, Ma X, Yuan Y, Li P, Wang H, et al. Esculetin Inhibits Proliferation, Migration, and Invasion of Clear Cell Renal Cell Carcinoma Cells. BioMed Pharmacother (2020) 125:110031. doi: 10.1016/j.biopha.2020.110031

328. Gong J, Zhang W, Feng XF, Shao MJ, Xing C. Aesculetin (6,7-Dihydroxyxcoumarin) Exhibits Potent and Selective Antitumor Activity in Human Acute Myeloid Leukemia Cells (THP-1) via Induction of Mitochondrial Mediated Apoptosis and Cancer Cell Migration Inhibition. J BUON (2017) 22:1563–9.

329. Karatup Kacar A, Bahadouri F, Kepecki Tekelli SE, Topcu G, Bolkent S. Investigation of Cell Death Mechanism and Activity of Esculetin-Loaded...
378. Surse VM, Gupta J, Tikoo K. Esculetin Induced Changes in Mmp13 and Bmp6 Gene Expression and Histone H3 Modifications Attenuate Development of Gliomerosclerosis in Diabetic Rats. J Mol Endocrinol (2011) 46:245–54. doi: 10.1530/JME-10-0154

379. Türk E, Ozan Tekeli I, Ozkan H, Uyar A, Cellat M, Kuzu M, et al. The Protective Effect of Esculetin Against Aluminum Chloride-Induced Reproductive Toxicity in Rats. Andrologia (2021) 53:e13930. doi: 10.1111/and.13930

380. Hongyan L. Esculetin Attenuates Th2 and Th17 Responses in an Ovalbumin-Induced Asthmatic Mouse Model. Inflammation (2016) 39:735–43. doi: 10.1007/s10753-015-0300-4

381. Leung KN, Leung PY, Kong LP, Leung P. Immunomodulatory Effects of Esculetin (6,7-Dihydroxycoumarin) on Murine Lymphocytes and Peritoneal Macrophages. Cell Mol Immunol (2005) 2:181–8.

382. Mabalarajan U, Dinda AK, Sharma SK, Ghosh B. Esculetin Restores Mitochondrial Dysfunction and Reduces Allergic Asthma Features in Experimental Murine Model. J Immunol (2009) 183:2059–67. doi: 10.4049/jimmunol.0900342

383. Sun B, Wang B, Xu M. Esculetin Inhibits Histamine-Induced Expression of Inflammatory Cytokines and Mucin in Nasal Epithelial Cells. Clin Exp Pharmacol Physiol (2019) 46:821–7. doi: 10.1111/1440-1681.13128

384. Baek JM, Park SH, Cheon YH, Ahn SJ, Lee MS, Oh J, et al. Esculetin Attenuates Receptor Activator of Nuclear Factor Kappa-B Ligand-Mediated Osteoclast Differentiation Through C-Fos/Nuclear Factor of Activated T-Cells C1 Signaling Pathway. Biochem Biophys Res Commun (2015) 461:334–41. doi: 10.1016/j.bbrc.2015.04.034

385. Na W, Lee EJ, Kang MK, Kim YH, Kim DY, Oh H, et al. Aesculetin Inhibits Reproductive Toxicity in Rats. JIR.S228361

386. Liu M, Li Y, Pan J, Liu H, Wang S, Ju D, et al. Effect of Esculetin on Bone Metabolism in Ovariectomized Rats. J Tradit Chin Med = Chung i Tsa Chih Ying Wen Pan (2018) 38:896–903.

387. Oral SA, Turkekul K, Gurur L, Guclu H, Erdogan S. Esculetin Protects Human Retinal Pigment Epithelial Cells From Lipopolysaccharide-Induced Inflammation and Cell Death. Curr Eye Res (2018) 43:1169–76. doi: 10.1080/02713683.2018.1481517

388. Jiang D, Hu J, Liu X. Topical Administration of Esculetin as a Potential Therapy for Experimental Dry Eye Syndrome. Eye (2017) 31:1724–32. doi: 10.1038/eye.2017.117

389. Elliott S, Rowan AD, Carrère S, Koshy P, Catterall JB, Cawston TE. Esculetin Inhibits Cartilage Resorption Induced by Interleukin 1α in Combination With Oncostatin M. Ann Rheum Dis (2001) 60:158–65. doi: 10.1136/ard.60.2.158

390. Hosseini A, Razavi BM, Banach M, Hosseinzadeh H. Quercetin and Hyperglycemia Through Activating Ampk in High-Fat Diet-Fed ICR Mice. J Clin Biochem Nutr (2020) 67:74–83. doi: 10.3164/jcbn.20-47

391. Dugher O, Mury P, Thimon-Trescases N, Noly PE, Thorin E, Carrier M. Therapeutic Potential of Quercetin to Alleviate Endothelial Dysfunction in Age-Related Cardiovascular Diseases. Front Cardiovasc Med (2021) 8:658400. doi: 10.3389/fcvm.2021.658400

392. Mirsafaei L, Reiner Ž, Shafabakhsh R, Asemi Z. Molecular and Biological Functions of Quercetin as a Natural Solution for Cardiovascular Disease Prevention and Treatment. Plant Foods Hum Nutr (2020) 75:307–15. doi: 10.1007/s11130-020-00832-0

393. Deng Q, Li XX, Fang Y, Chen X, Xue J. Therapeutic Potential of Quercetin as an Antithrombotic Agent in Atherosclerotic Cardiovascular Disease: A Review. Evidence-Based Complement Altern Med (2020) 2020:5926381. doi: 10.1155/2020/5926381

394. Dabeek WM, Marra MV. Dietary Quercetin and Kaempferol: Bioavailability and Potential Cardiovascular-Related Bioactivity in Humans. Nutrients (2019) 11:2288. doi: 10.3390/nu1102288

395. Ferencyzova K, Kalocayova B, Bartekova M. Potential Implications of Quercetin and Its Derivatives in Cardioprotection. Int J Mol Sci (2020) 21:1585. doi: 10.3390/ijms21051585

396. Faragali H, Kemelo MK, Canova NK. SIRT1 Modulators in Experimentally Induced Liver Injury. Oxid Med Cell Longev (2019) 2019:8767594. doi: 10.1155/2019/8767594

397. Bae M, Park YK, Lee JY. Food Components With Antiinfective Activity and Implications in Prevention of Liver Disease. J Nutr Biochem (2018) 55:1–11. doi: 10.1016/j.jnutbio.2017.11.003

398. Almatroodi SA, Alsalhi MA, Almotaroudi A, Verma AK, Aloliqi A, Allemaim KS, et al. Potential Therapeutic Targets of Quercetin, a Plant Flavonol, and Its Role in the Therapy of Various Types of Cancer Through the Modulation of Various Cell Signaling Pathways. Molecules (2021) 26:1315. doi: 10.3390/molecules26051315

399. Orfali G di C, Duarte AC, Bonadio V, Martinez NP, de Araujo MEMB, Priviero FB, et al. Review of Anticancer Mechanisms of Isoquercitin. World J Clin Oncol (2016) 7:189–99. doi: 10.5360/wjco.v7.i2.189

400. Jantan I, Haque MA, Arshad L, Harikrishnan H, Septama AW, Mohamed-Hussein ZA, Dietary Polyphenols Suppress Chronic Inflammation by Modulation of Multiple Inflammation-Associated Cell Signaling Pathways. J Nutr Biochem (2021) 93:108634. doi: 10.1016/j.jnutbio.2021.108634

401. Wang Y, Tao B, Yan W, Sun Y, Wang L, Sun J, et al. Drug Delivery Based Pharmacological Enhancement and Current Insights of Quercetin With Therapeutic Potential Against Oral Diseases. BioMed Pharmacother (2020) 128:103772. doi: 10.1016/j.biopharm.2020.110372

402. Huang YY, Wang ZH, Deng LH, Wang H, Zheng Q. Oral Administration of Quercetin or Its Derivatives Inhibit Bone Loss in Animal Model of Osteoporosis. Oxid Med Cell Longev (2020) 2020:6308597. doi: 10.1155/2020/6308597

403. Ghorbani A. Mechanisms of Antidiabetic Effects of Flavonoid Rutin. BioMed Pharmacother (2017) 96:305–12. doi: 10.1016/j.biopharm.2017.10.001

404. Habtemariam S, Lentini G. The Therapeutic Potential of Rutin for Diabetes: An Update. Mini-Rev Med Chem (2015) 15:524–8. doi: 10.2174/13895751501504210372

405. Hosseinzadeh H, Nassiri-Ad M. Review of the Protective Effects of Rutin on the Metabolic Function as an Important Dietary Flavonoid. J Endocrinol Invest (2017) 37:783–8. doi: 10.1007/s40618-014-0096-3

406. Lim SH, Yu JS, Lee HS, Choi CI, Kim KH, Antidiabetic Flavonoids From Fruits of Morus Alba Promoting Insulin-Stimulated Uptake Via akt and Amp-Activated Protein Kinase Activation in 313-L1 Adipocytes. Pharmaceutics (2021) 13:526. doi: 10.3390/pharmaceutics13040526

407. Xuan Y, Wei X, You H, Yuan H, Lee HJ, Dong M, et al. Rutin Ameliorates Obesity Through Brown Fat Activation. FASEB J (2017) 31:33–45. doi: 10.1096/fj.20160459RR

408. Liang W, Zhang D, Kang J, Meng X, Yang J, Yang L, et al. Protective Effects of Rutin on Liver Injury in Type 2 Diabetic Db/Db Mice. BioMed Pharmacother (2018) 107:721–8. doi: 10.1016/j.biopha.2018.08.046

409. Mainzen Prince PS, Kamalakannan N. Rutin Improves Glucose Homeostasis in Streptozotocin Diabetic Mice by Altering Glycyltic and Gluconeogenic Enzymes. J Biochem Mol Toxicol (2006) 20:96–102. doi: 10.1002/jbt.20117
and Diabetes. Prep Biochem Biotechnol (2020) 50:969–78. doi: 10.1080/
10826068.2020.1786699
454. Fariq) Pereiss R, Park CS, Park Y. Mechanisms of Action of Coffee Bioactive
Components on Lipid Metabolism. Food Sci Biotechnol (2019) 28:1287–96. 
doi: 10.1007/s10060-019-00662-0
455. Yamagata K. Do Coffee Polyphenols Have a Preventive Action on Metabolic
Syndrome Associated Endothelial Dysfunctions? An Assessment of the
Current Evidence. Antioxidants (2018) 7:26. doi: 10.3390/antiox7020026
456. Ali SS, Ahmad WANW, Budin SB, Zainalabidin S. Implication of Dietary
Phenolic Acids on Inflammation in Cardiovascular Disease. Rev Cardiovasc 
Med (2020) 21:225–40. doi: 10.1083/j.rcm.2020.02.49
457. Silva H, Lopes NMF. Cardiovascular Effects of Caffeic Acid and Its 
Derivatives: A Comprehensive Review. Front Physiol (2020) 11:395516. 
doi: 10.3389/fphys.2020.595516
458. Li L, Su C, Chen X, Wang Q, Jiao W, Luo H, et al. Chlorogenic Acids in 
Cardiovascular Disease: A Review of Dietary Consumption, Pharmacology, 
and Pharmacokinetics. J Agric Food Chem (2018) 66:6464–84. doi: 10.1021/ 
acs.jafc.0c01554
459. Choi J, Park JK, Lee KT, Park KK, Kim WB, Lee JH, et al. In Vivo 
Antipathotopic Effects of Liguaria Ficiheri Var. Specifomis and the 
Identification of the Active Component, 3,4-Dicaffeoylquinic Acid. J Med 
Food (2005) 8:348–52. doi: 10.1089/jmf.2005.8.348
460. Monteiro Espindola KM, Ferreira RG, Mosquera Narvaez LE, Rocha Silva 
Rosario AC, Machado Da Silva AH, Bispo Silva AG, et al. Chemical and 
Pharmacological Aspects of Caffeic Acid and Its Activity in 
Hepatocarcinoma. Front Oncol (2019) 9:951. doi: 10.3389/fonc.2019.00951
461. Buldak RJ, Hejmo T, Osowski M, Buldak L, Kulda M, Polanik R, et al. 
The Impact of Coffee and Its Selected Bioactive Compounds on the Development 
and Progression of Colorectal Cancer In Vivo and In Vitro. Molecules (2018) 
23:3309. doi: 10.3390/molecules23123309
462. Liang N, Kitts DD. Role of Chlorogenic Acids in Controlling Oxidative 
and Inflammatory Stress Conditions. Nutrients (2015) 7(1):16. doi: 10.3390/ 
nutrients7010016
463. Kim H, Lee YS. Identification of New Dicaffeoylquinic Acids From 
Chrysanthemum Mortifolium and Their Antioxidant Activities. Planta 
Med (2005) 71:871–6. doi: 10.1055/s-2005-873115
464. Izuta H, Narahara Y, Shimazawa M, Mishima S, Kondo SI, Hara H. 1,1-
Diphenyl-2-Picrylhydrazyl Radical Scavenging Activity of Bee Products and 
Their Constituents Determined by ESR. Biol Pharm Bull (2009) 32:1947–51. 
doi: 10.1248/bpb.32.1947
465. Fukutomi R, Oishi T, Koyama Y, Pervin M, Nakamura Y, Isemura M. 
Beneficial Effects of Epigallocatechin-3-O-Gallate, Chlorogenic Acid, 
Resveratrol, and Curcumin on Neurodegenerative Diseases. Molecules 
(2015) 20:3423. doi: 10.3390/molecules20093423
466. Habtemariam S. Protective Effects of Caffeic Acid and the Alzheimer’s Brain; 
An Update. Mini-Rev Med Chem (2016) 17:667–74. doi: 10.2174/ 
13895575166113000947
467. Socala K, Szaopa A, Serefsko A, Poleksaz E, Wlaz P. Neutrophoretic Effects of 
Coffee Bioactive Compounds: A Review. Int J Mol Sci (2020) 22:11–64. 
doi: 10.3390/ijms22010107
468. Khan F, Banumaurachchi NI, Tabassum N, Kim YM. Caffeic Acid and Its 
Derivatives: Antimicrobial Drugs Toward Microbial Pathogens. J Agric Food 
Chem (2021) 69(10):2979–3004. doi: 10.1021/acs.jafc.0c07579
469. Godlewka-lykówicz B, Świslocka R, Kalinowska M, Golonko L, Świderski 
G, Arziczewska Z, et al. Biologically Active Compounds of Plants Structure-
Related Antioxidant, Microbiological and Cytotoxic Activity of Selected 
Carboxylic Acids. Mater (Basel) (2020) 1:31–37. doi: 10.3390/ 
ma13194454
470. Zhao Y, Geng CA, Ma YB, Huang XY, Chen H, Cao TW, et al. UFLC/MS-IT-
TOF GUIDED Isolation of Anti-HBV Active Chlorogenic Acid Analogues From 
Artemisia Capitella as a Traditional Chinese Herb for the Treatment of 
Hepatitis. J Ethnopharmacol (2014) 156:147–54. doi: 10.1016/j.
jep.2014.08.043
471. Yang ZZ, Yu YT, Lin HR, Liao DC, Cui XH, Wang HB. Lonicera Japonica 
Extends Lifespan and Healthspan in Caenorhabditis Elegans. Free Radic Biol 
Med (2018) 129:310–22. doi: 10.1016/j.freeradbiomed.2018.09.035
472. Ikeda R, Yanagisawa M, Takahashi N, Kawa T, Kumazawa S, Yamato 
N, et al. Brazilian Propolis-Derived Compounds inhibit TNF-β-Mediated 
Downregulation of Adiponectin Expression via Different Mechanisms in
563. Kitamura H, Naoe Y, Kimura S, Miyamoto T, Okamoto S, Toda C, et al. Beneficial Effects of Brazilian Propolis on Type 2 Diabetes in Ob/Ob Mice. _Adipocyte_ (2013) 2:227–36. doi: 10.4161/adip.25608

564. Munakata R, Takemura T, Tatsumi K, Moriyoshi E, Yanagihara K, Sugiyama A, et al. Isolation of Artemisia Capillaris Membrane-Bound Di-Prenyltransferase for Phenylpropanoids and Redesign of Artepillin C in Yeast. _Commun Biol_ (2019) 2:384. doi: 10.1038/s42003-019-0630-0

565. Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the Use of Complementary Health Approaches Among Adults: United States, 2002–2012. _Natl Health Stat Rep_ (2015) (79):1–16.

566. Britton ER, Kellogg JJ, Kvalheim OM, Cech NB. Biochemometrics to Identify Synergists and Additives From Botanical Medicines: A Case Study With Hydrastis Canadensis (Goldenseal). _J Nat Prod_ (2018) 81:484–93. doi: 10.1021/acs.jnatprod.7b00654

567. Sorkin BC, Kuszak AJ, Bloss G, Fukagawa NK, Hoffman FA, Jafari M, et al. Improving Natural Product Research Translation: From Source to Clinical Trial. _FASEB J_ (2020) 34:41–65. doi: 10.1096/f.201902143R

568. Logendra S, Ribnicky DM, Yang H, Poulev A, Ma J, Kennelly EJ, et al. Bioassay-Guided Isolation of Aldose Reductase Inhibitors From Artemisia Dracunculus. _Phytochemistry_ (2006) 67:1539–46. doi: 10.1016/j.phytochem.2006.05.015

569. Eisenman SW, Poulev A, Struwe L, Raskin I, Ribnicky DM. Qualitative Variation of Anti-Diabetic Compounds in Different Tarragon (Artemisia Dracunculus L.) Cytotypes. _Fitoterapia_ (2011) 82:1062–74. doi: 10.1016/j.fitote.2011.07.003

570. Baell JB. Feeling Nature’s PAINS: Natural Products, Natural Product Drugs, and Pan Assay Interference Compounds (PAINS). _J Nat Prod_ (2016) 79:616–28. doi: 10.1021/acs.jnatprod.5b00947

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.