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Review Article

Pharmacological Activities and Pharmacokinetics of Rutaecarpine

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Abstract

Rutaecarpine, a representative alkaloid, has been obtained from *Euodia rutaecarpa* (Juss.) Benth., a well-known traditional Chinese medicine. Research has demonstrated that rutaecarpine possesses a diverse array of pharmacological activities, including exerting impacts on the cardiovascular system, as well as anti-inflammatory, anti-tumor, and hepatoprotective properties. However, as research has progressed, the poor water solubility of rutaecarpine has become a significant limiting factor. This leads to poor absorption in the body after oral administration, resulting in lower free drug concentration and ultimately decreased bioavailability. This comprehensive review of rutaecarpine's pharmacological profile, pharmacokinetics, and formulation design provides valuable insights for future research and its potential therapeutic applications.

Introduction

Euodia rutaecarpa is obtained from the dried, nearly mature fruit of *Evodia rutaecarpa* (Juss.) Benth. This ancient Chinese ethnomedicine is used to dispel cold, relieve pain, alleviate adverse qi, stop vomiting, and treat dirrhea.[1] Extensive modern pharmacological research has established that Euodia rutaecarpa exhibits a remarkable array of biological activities. Notably, it shows promise in combatting Alzheimer's disease, possesses powerful anti-inflammatory properties, and demonstrates significant oncostatic effects. Furthermore, this versatile herb offers analgesic and antibacterial benefits, along with antihypertensive and vasodilatory effects.[2-4] *Euodia rutaecarpa* is increasingly recognized for its valuable applications across diverse fields such as medicine, cosmetics, food, and veterinary care, showcasing its significance and versatility on a global scale. It is particularly noted in the medical field for treating various conditions, including headaches, menorrhagia, dermatophytosis, abdominal pain, and vomiting.[5]

Euodia rutaecarpa contains various chemical constituents, including alkaloids, terpenoids, flavonoids, and volatile oils. The primary active compounds in *Euodia rutaecarpa* are evodiamine and rutaecarpine (Rut, Figure 1).[6] In 1915, Asahina and Kashiwaki successfully isolated rut from acetone extracts of the remarkable plant *Evodia rutaecarpa*, marking a significant advancement in the study of this compound.[7] Rut, a remarkable indolopyridoquinazoline alkaloid extracted from *Evodia rutaecarpa*, demonstrates diverse and potent biological and pharmacological effects in vivo, modulating various functions through intricate molecular pathways. These effects include anti-inflammatory, anti-platelet, vasodilatory, analgesic, cytotoxic, anti-Alzheimer's disease, and anti-adiposity actions,[6] as well as anti-diabetic potential,[8,9] among its most significant therapeutic effects. However, the poor water solubility, moderate potency, and cytotoxicity of rut limit its direct clinical application.[10] Rut undergoes metabolism in vivo primarily through hydroxylation and glucuronidation, which are mediated by the enzymatic pathways of cytochrome P450 and UDP-glucuronosyltransferase.[11] Several reviews of rut have been published in recent years. In 2008, the review on rut's metabolism, pharmacological effects, structure-activity relationship (SAR) studies, synthesis, and isolation was comprehensively updated by Lee et al.[2] In 2010, Jia and Hu summarized the cardiovascular-protective pharmacological activities of the substance.[12] In 2015, Son et al reviewed the synthesis, biological activity, and SAR of rut derivatives.[13] Four years later, an updated review by Tian et al on rut's promising cardiovascular-protective potential is slated for publication.[6] In 2020, Li et al critically appraised recent progress regarding rut as a prospective hepatoprotectant.[14] Li et al have recently

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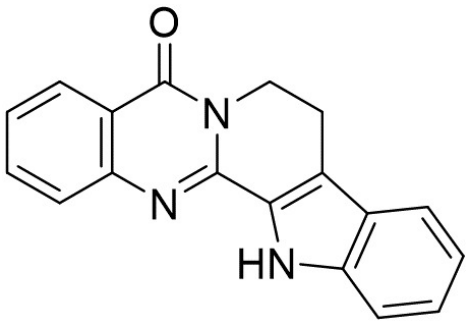

Figure 1. Rutaecarpine

delivered a compelling and thorough examination of rut derivatives, showcasing their remarkable and diverse bioactivities.[10] The previous reviews focused on a limited range of pharmacological effects, such as cardiovascular and liver-protective activities, and did not include recent research.

In this paper, we explore the diverse and intriguing pharmacological activities, pharmacokinetics, and formulation design of rut, with the goal of providing a comprehensive reference for further investigation into this compound.

Search strategies

For this review, searches were conducted across various electronic databases, including PubMed, Web of Science, China National Knowledge Infrastructure, Scopus, Embase, Google Scholar, and Sci-Finder Scholar. A search on the compound rut conducted using various keyword combinations included "rutaecarpine," "*Euodia rutaecarpa*," "wu zhu yu," "chemical compositions of alkaloids in Euodia rutaecarpa," "pharmacological activity," "physicochemical properties," "pharmacokinetics," and "toxicity." This review is available only in Chinese and English due to language limitations. In this study, we will review existing research on the pharmacological activity, pharmacokinetics and preparation direction of rut, and explore its potential mechanisms to provide reference for the subsequent clinical translation.

Physicochemical properties

Rut is a lipophilic compound that shows high lipid solubility, indicated by a log P value of 3.2.[15] Its physical properties include a molecular weight of 287.321 g/mol, a 260-262 °C melting point, and a 1.43 g/cm^3 density. Oil-water partition coefficients of 2.03 for the aqueous phase, 2.73 at pH 5.5, and 2.74 at pH 7.4 were furthermore predicted by the PhysChem Module of the ACD/Labs Percepta Platform. The log Kow-based (WSKOW v1.41) estimate for water solubility is 4.11 mg/L at 25 °C, while the fragment-based estimate is 3.8961 mg/L. The rut content in various varieties of Euodia rutaecarpa has been analyzed using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). The raw products of Wuzhuyu (Euodiae Fructus) contained 0.070% (w/w) of rut, while five processed products exhibited rut levels of 0.065% (w/w), 0.065% (w/w), 0.063% (w/w), 0.064% (w/w), and 0.078% (w/w), respectively.[16] According to the Biopharmaceutics Classification System (BCS), rut is classified as a type II drug. Its drug-forming properties are suboptimal, significantly impacting its pharmacokinetic characteristics and leading to poor bioavailability in vivo following oral administration.

Pharmacological activity

Anti-cardiovascular diseases

Cardiovascular disease remains a significant global health issue, comprising a variety of conditions such as heart failure, hypertensive heart disease, angina pectoris, myocardial infarction, rheumatic heart disease, arrhythmia, peripheral artery disease, and venous thrombosis.[17] Extensive experimental research has illustrated the potential of rut in treating cardiovascular diseases. For instance, rut has been shown to inhibit cardiomyocyte hypertrophy,[18] alleviate diabetic cardiomyopathy,[8] and exhibit anti-diabetic,[19] anti-platelet aggregation,[20] anti-hypertensive,[21] and anti-atherosclerotic effects.[22] The primary molecular targets of rut include calcitonin gene-related peptide (CGRP), transient receptor potential vanilloid 1 (TRPV1), ATP-binding cassette transporter A1 (ABCA1), AMP-activated protein kinase (AMPK), and the β1-adrenergic receptor (β1-AR).[6]

Cardiac action

The findings from preclinical studies on cardiac protection are presented in Table 1. Cardiac hypertrophy is a vital adaptive response of the heart that occurs under conditions of high hemodynamic stress. By enhancing cardiac function, this mechanism not only improves the heart's efficiency but also alleviates ventricular wall tension and lowers the oxygen consumption of myocytes.[23] Myocardial hypertrophy has two categories, which can be grouped into physiological and pathological hypertrophy. Physiological hypertrophy is typically mild and reversible, often resulting from factors such as exercise or pregnancy.[24] In contrast, chronic long-term conditions characterized by high circulatory stress, such as hypertension and valvular heart disease, can lead to pathological myocardial hypertrophy. This condition is characterized by excessive ventricular enlargement, myocardial dysfunction, and fibrosis.[25] A serious medical condition that can lead to heart failure and sudden death is cardiac hypertrophy. Li et al demonstrated that administering rut (at doses of 20 or 40 mg/kg/day, via intragastric route) for four weeks in rats with cardiac hypertrophy led to increased levels of angiotensin II. Additionally, the left ventricular tissue showed enhanced mRNA expression and activity of calcineurin following the development of cardiac hypertrophy.[21] Rut has been shown to improve cardiac hypertrophy in rats subjected to pressure overload, particularly in a model of hypertensive cardiac hypertrophy induced by abdominal aortic constriction (AAC). Zeng et al found that rut

Table 1. Rut: Summary of preclinical study results on cardiac protection

Model type	Dosage	Target/Pathway	Study result
Rat model of cardiac hypertrophy	20, 40 mg/kg/day, intragastric administration, continuous for 4 weeks	Angiotensin II, calcineurin	Increased angiotensin II levels, enhanced calcineurin mRNA expression and activity in left ventricular tissue
Rat model of hypertensive cardiac hypertrophy induced by abdominal aortic constriction (AAC)	Not specified	Nox4-ROS-ADAM17 pathway, ERK1/2 pathway	Inhibited the Nox4-ROS-ADAM17 pathway, prevented excessive activation of the ERK1/2 pathway, and effectively alleviated hypertensive cardiac hypertrophy
High-glucose (30 mM)-induced myocardial injury cell model	Not specified	Mitogen-activated protein kinase (MAPK) pathway	Regulated the expression of the MAPK pathway, reduced cell apoptosis, oxidative stress and inflammatory response, and significantly alleviated myocardial injury caused by high glucose
Rat model of isoprenaline-induced acute myocardial ischemic injury	100 mg/kg, administration route not specified	Not specified (associated with myocardial ischemic injury repair)	Effectively mitigated acute myocardial ischemic injury
Not specified (in vitro/in vivo)	Not specified	TRPV1, Ca^{2+}/CaMKII, CaM/CaMKKβ/AMPK, eNOS	Promoted eNOS phosphorylation and NO synthesis via TRPV1-mediated activation of Ca^{2+}/CaMKII and CaM/CaMKKβ/AMPK signaling pathways
Doxorubicin (DOX)-induced cardiac injury model (in vitro/in vivo)	Not specified	AKT signaling pathway	Activated the AKT signaling pathway, and reduced DOX-induced oxidative damage and cardiomyocyte apoptosis

effectively reduced hypertensive cardiac hypertrophy by inhibiting the Nox4-ROS-ADAM17 pathway and preventing the overactivation of the ERK1/2 pathway.[26] In the development of heart failure associated with cardiovascular diseases, cardiomyocyte damage is a critical factor, particularly relevant in diabetic cardiomyopathy, a common complication of diabetes.[27] Regulating how cells adapt to stress stimuli is what the mitogen-activated protein kinase (MAPK) signaling pathway is responsible for.[28] Furthermore, abnormal activation of this pathway is prevalent in cardiovascular pathologies, and inhibiting it has been shown to halt the progression of diabetic cardiomyopathy.[29] In the context of treating diabetic cardiomyopathy, MAPK signaling represents a significant target for herbal medicine.[30] Recent research compellingly demonstrates that rut plays a pivotal role in influencing the expression of the MAPK pathway in myocardial cells affected by high glucose levels (30 mM glucose). By effectively reducing apoptosis, oxidative stress, and inflammatory responses, rut significantly mitigates the damage inflicted by elevated glucose, offering a promising avenue for therapeutic intervention.[31] Additionally, Sun et al demonstrated that rut (100 mg/kg) effectively mitigated isoprenaline-induced acute myocardial ischemic injury in rats.[32] Lee et al compellingly demonstrate that rut significantly enhances the synthesis of nitric oxide (NO) and fosters the phosphorylation of endothelial nitric oxide synthase (eNOS). This process occurs through the dynamic interplay of the Ca^{2+}/CaMKII and CaM/CaMKK beta/AMPK signaling pathways, with transient receptor potential vanilloid 1 (TRPV1) playing a crucial role.[33] Doxorubicin (DOX) is the preferred treatment for patients with severe leukemia, lymphoma, or solid tumors.[34] However, cardiotoxicity is a significant side effect that limits its clinical use, and the cardiac damage it causes is irreversible.[35] Liao et al activated the AKT signaling pathway to mitigate DOX-induced oxidative damage and apoptosis in both in vivo and in vitro assays.[36] These studies suggest that for preventing and treating cardiac hypertrophy, rut may be an effective option.

Effects on blood vessels

Rut demonstrates significant vasoprotective effects, and its vasoprotective and antihypertensive properties have been extensively studied. Vascular aging represents a critical pathological transformation in the emergence and progression of cardiovascular disorders, including hypertension and atherosclerosis.[6] This process is characterized by alterations in vascular structure and function, such as increased intima-media thickness of arteries, reduced compliance, and vascular inflammation.[37] Vascular aging is closely associated with the senescence of the cells that comprise the vessel wall, wherein senescent vascular smooth muscle cells (VSMCs) exhibit dysfunctions, including impaired migration, phenotypic transformation, and differentiation into osteoblast-like cells, which contribute to the acceleration of vascular calcification.[38] Angiotensin II (Ang II) is a key component of the renin-angiotensin system and significantly contributes to vascular aging, influenced by factors such as hypertension and the natural aging process.[39] Sirtuin 1 (SIRT1), a NAD^+-dependent histone deacetylase that is involved in regulating numerous metabolic activities within cells, particularly in cellular senescence, is recognized as a longevity protein.[40] Substantial evidence suggests that the primary cardiovascular effects of rut are linked to the TRPV1 receptor.[6] Research has demonstrated that rut mitigates hypertension-induced vascular remodeling and significantly inhibits Ang II-induced proliferation and phenotypic switching of VSMCs.[41] Furthermore, it has been reported that rut upregulates SIRT1 expression and inhibits Ang II-induced senescence and migration of VSMCs through a mechanism that involving the activation of the TRPV1/AMPK signaling pathway.[42] Additionally, by upregulating SIRT1 expression, rut inhibits the calcification of VSMCs.[43] It was also found that rut upregulates SIRT1 expression and prevents high glucose-

induced senescence in endothelial cells, which is associated with the activation of the TRPV1/[Ca^{2+}]i/CaM signaling pathway.[44] The AKT signaling pathway plays a crucial role in regulating cell proliferation, glucose metabolism, oxidative stress, and autophagy.[45] Furthermore, it has been documented that rut mitigates doxorubicin-induced cardiac impairment and cell death in vitro by inhibiting of oxidative stress and enhancing antioxidant capacity. Research has shown that rut activates AKT and Nrf2, which leads to the upregulation of antioxidant enzymes, such as GCLM and HO-1.[28] Dysfunction in VSMCs is associated with overexpression of Connexin 43 (Cx43). A study by Wang et al showed that through the TRPV1/[Ca^{2+}]i/CaM/NF-κB signaling pathway, rut inhibits Cx43 overexpression, thereby preventing ox-LDL-induced VSMC dysfunction.[46] Additionally, rut has been shown to mitigate microvascular thrombosis in mice and inhibit platelet activation in humans via the PI3K/Akt/GSK3β signaling pathway.[20] These findings suggest that a potential candidate for the prevention and treatment of vascular disorders could be rut.

Anti-diabetic

As a chronic, lifelong disease affecting individuals of all ages and genders, diabetes requires ongoing treatment. Its significant impact on quality of life and the rising global prevalence have made it a major public health concern.[47] The global medical research community, the World Health Organization, and society at large are becoming increasingly aware of the seriousness of its complications.[48] Type 2 diabetes, characterized by elevated blood glucose levels resulting from insulin resistance and β-cell dysfunction, is a chronic metabolic disorder.[49] Demonstrated that rut possesses anti-diabetic properties in high-fat diets, in mice with streptozotocin-induced type 2 diabetes, and in in vitro models by modulating hepatic glucose homeostasis. According to Zuo et al, diabetic nephropathy (DN) is a significant microvascular complication associated with diabetes mellitus.[50] Furthermore, Chen et al were the first to report that rut alleviates DN by suppressing extracellular matrix (ECM) production and inflammation in high-glucose (HG)-treated SV40 cells.[51] This effect is effectively achieved by suppressing the activation of the TGF-β1/Smad3 and NF-κB signaling pathways, coupled with a targeted approach towards CK2α, leading to significant outcomes.

Anti-platelet aggregation

Anucleate blood cells known as platelets play a crucial role in thrombotic and hemostatic processes. A variety of cardiovascular and cerebrovascular diseases can be caused by intravascular thrombosis.[52] Antiplatelet drugs have been shown to significantly lower the risk of cardiovascular diseases (CVDs). The involvement of activated platelets in both acute and chronic CVDs is well established, as noted by Huang et al. Additionally, rut inhibits human platelet activation and reduces microvascular thrombosis in mice through the PI3K/Akt/GSK3β signaling pathway.[20] Furthermore, Huang et al showed that rut suppresses platelet aggregation by inhibiting the NF-κB pathway, specifically by reversing IκBα degradation as well as blocking IKK, IκBα, and p65 phosphorylation.[53]

Anti-hypertension

Hypertension is a significant risk factor that can lead to a range of serious medical conditions, including stroke, hypertensive heart disease, coronary artery disease, nephropathy, and aneurysms. Addressing hypertension is crucial for protecting your health and preventing these potentially life-threatening issues.[54] CGRP, recognized as the strongest vasodilator, is vital in hypertension development.[55] TRPV 1 and transient receptor potential ankyrin 1 (TRPA 1) play a crucial role in the synthesis and release of CGRP, which modulates cardiovascular tone (see Figure 2). Rut demonstrates significant vasodilatory and antihypertensive effects by stimulating the synthesis and release of CGRP through TRPV1 activation.[47]

Anti-obesity

As living standards continue to improve and dietary habits evolve, the prevalence of obesity has been increasing, creating a significant public health concern. Obesity is increasingly recognized as a significant factor contributing to various chronic diseases, such as diabetes and hypertension. Obesity is fundamentally driven by an imbalance between calorie consumption and energy expenditure, leading to excessive fat accumulation and significant disruptions in the endocrine system. This imbalance underscores the critical importance of maintaining a healthy lifestyle to prevent serious health consequences.[56] Liu et al showed that rut enhances the browning of white adipocytes by activating the AMPK-PRDM16 pathway.[57] Furthermore, rut has been shown to activate thermogenesis in brown and beige adipose tissue, counteracting diet-induced obesity via the AMPK pathway.[58]

Anti-inflammation

Inflammation represents a complex process within the immunological milieu and is a protective immune response of the body.[59] Upon recognizing inflammatory signals, cell surface receptors initiate a series of intracellular signaling pathways that regulate the expression of both upstream and downstream signaling genes, leading to an increased release of inflammatory cytokines. Rut has the potential to reduce the severity and duration of inflammatory cascade activation by modulating the expression of inflammatory factors. NF-κB is a crucial nuclear transcription factor in cells that activates several pathways necessary for essential cellular functions, including immune and inflammatory responses, regulation of apoptosis, and stress responses.[60] By suppressing the NF-κB pathway, rut is capable of inhibiting the expression of related inflammatory factors, thereby exhibiting anti-inflammatory properties.[61] Rut has

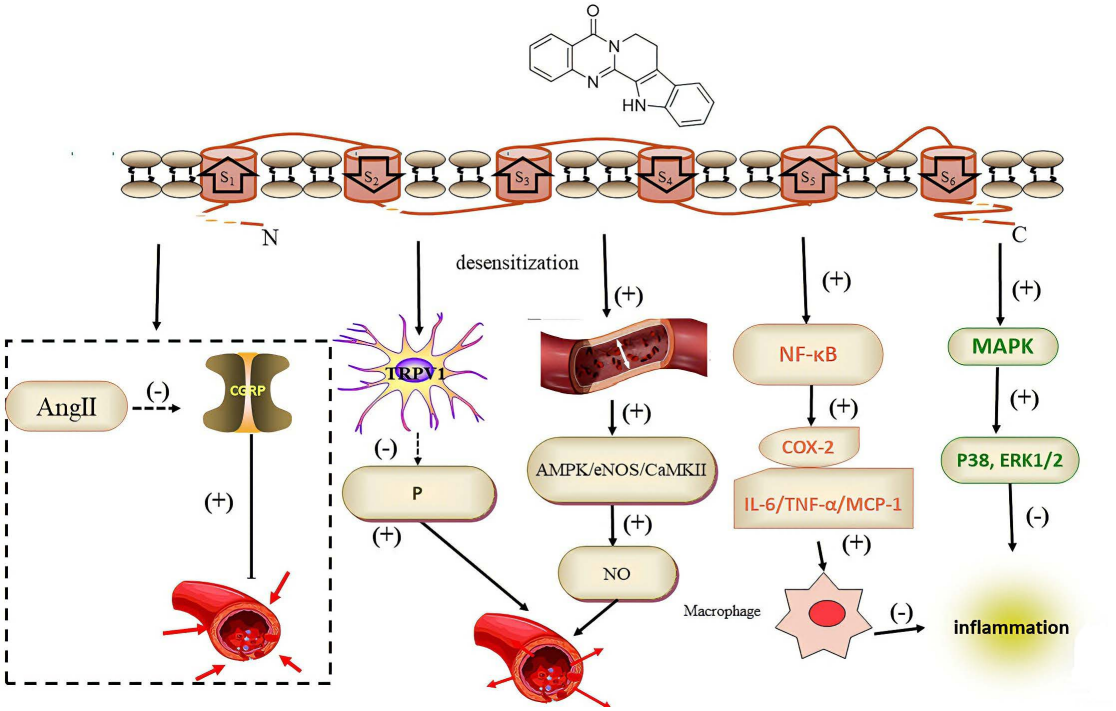

Figure 2. The mechanism of rutaecarpine for anti-hypertensive and anti-tumour

been shown to exert anti-inflammatory effects primarily by modulating the NF-κB and ERK/p38 molecular signaling pathway.[62] Additionally, by inhibiting the PI3K/Akt/NF-κB and MAPK signal transduction pathways, rut has been demonstrated to reduce inflammation in RAW 264.7 macrophages.[63] Osteoarthritis (OA) is a chronic, progressive joint disease commonly observed in the elderly, characterized by inflammation and degeneration of cartilage. Disruption of the metabolic pathways of articular cartilage serves as the primary impetus for the progression of osteoarthritis. Furthermore, inflammation is a substantial contributing factor to the advancement of OA.[64] Rut has also been reported to have potential in treating synovitis associated with rheumatoid arthritis.[65] Rut has been shown to have anti-inflammatory and anticatabolic effects in IL-1β-stimulated chondrocytes by inhibiting the activation of the PI3K/Akt/NF-κB and MAPK signaling pathways through integrin αVβ3.[66] Additionally, a previous study showed that rut effectively inhibits the formation of osteoclasts by interfering with the pathways activated by macrophage-stimulating factor and receptor activator of NF-κB.[67] Huang et al revealed that rut improves outcomes in acute pancreatitis by inhibiting the MAPK and NF-κB signaling pathways.[68] The release and mediation of CGRP have been confirmed as the molecular targets of most pharmacological effects of rut. Research indicates that rut, through VR1 activation, increases the release of endogenous CGRP, enhances pancreatic tissue microcirculation, and modulates the expression of inflammatory factors, thereby preventing acute pancreatitis in rats.[69] Additionally, rut can intervene in ulcerative colitis by regulating the synthesis and release of CGRP.[70] The study results showed that rut could lower the expression levels of IL-6, IL-1β, and TNF-α in the serum of mice with ulcerative colitis. This effect occurs by downregulating the TGF-β1/Smad3 pathway, which is a downstream signaling molecule of TGF-β involved in regulating inflammation and the formation of fibrosis. This action alleviates the clinical manifestations associated with inflammation.[71] Specific dermatitis is characterized by chronic, non-specific inflammation of the skin, with one of the primary causes being the imbalance between T helper lymphocytes 1 (Th1) and Th2. The IL-4 signaling pathway and the STAT6 transcription factor are essential for regulating the balance between Th1 and Th2 cells.[72] Research has shown that rut can decrease the expression of IL-4, IL-5, and IgE in the serum of mice with specific dermatitis through the IL-4/STAT6 pathway. The compound can enhance interferon gamma (IFN-γ) expression, promote Th1 and Th2 cell balance, reduce inflammatory cell infiltration, and improve skin structure integrity.[73] Xu et al discovered that rut upregulates the expression of Sirtuin 6 (SIRT6), resulting in increased H3K9 deacetylation and inhibition of NF-κB transcriptional activation in vitro, thereby mediating the inflammatory response.[74] Modulating the Nrf2/heme oxygenase-1 and ERK1/2 signaling pathways has been shown to significantly diminish apoptosis and reduce the production of inflammatory cytokines in cases of neuronal injury, highlighting their critical role in neuroprotection.[75] Rut powerfully disrupts the interaction between Keap1 and Nrf2, leading to the activation of Nrf2 and significantly reducing the severity of colitis caused by dextran sulfate sodium.[76] Rut alleviates cognitive impairment, enhances the morphology and quantity of nerve cells, reduces neuroinflammatory responses, and mitigates LPS-induced inflammation in BV2 microglial

cells in mice. Hu et al demonstrated that rut can reduce cellular damage by downregulating the expression of brain IL-6, IL-1β, and TNF-α, which improves learning and memory deficits in C57BL/6N mice.[77] Additionally, rut lessens glomerular podocyte injury by inhibiting renal inflammation and pyroptosis via the VEGFR2/NLRP3 pathway.[78] Moreover, rut inhibits ER stress-mediated caspase-12 and NF-κB pathways, reducing sepsis-induced apoptosis and inflammatory responses in peritoneal resident macrophages.[79] Zhang et al reported that rut alleviates LPS-induced damage to lung cells.[80] This effect is achieved by activating the AMPK/SIRT1 signaling pathway while inhibiting inflammation, oxidative stress, apoptosis, and ER stress. Figure 2 illustrates the mechanism of action. COVID-19, caused by SARS-CoV-2, has led to millions of deaths and significant socioeconomic disruption since its emergence in 2019.[81] Lin et al confirmed that treatment with rut inhibits the inflammatory responses associated with COVID-19 and SARS-CoV-2 infection.[82] Li et al proposed that rut may enhance psoriasis symptoms by restoring gut microbiota balance and diminishing inflammatory cytokine production.[83]

Anti-tumor

A severe disease that threatens the health and lives of individuals worldwide is cancer.[84] It has become a focal point of research aimed at identifying components with effective anticancer properties derived from natural products. Rut has been reported to display a diverse array of antitumor biological activities. Chan et al found that rut significantly decreased tumor size in BALB/c nude mice with xenograft tumors.[85] Additionally, it markedly decreased the cell viability of colon cancer cell lines, such as HCT-116 and SW480, in a concentration-dependent manner, while also inhibiting cell proliferation, migration, and invasion. Furthermore, the NF-κB/STAT3 signaling pathway was inhibited through the upregulation of cleaved Caspase-3 expression and the downregulation of Bcl-2 expression, which promoted apoptosis in HCT-116 and SW480 colorectal tumor cells. As reported by Byun et al, rut's anti-proliferative activity in human colorectal cancer cells is intricately linked to the reduced expression of the Wnt/β-catenin signaling pathway's target genes and the blockade of the pathway itself.[86] Further investigations have shown that rut also triggers G0/G1 cell-cycle arrest and induces apoptotic cell death, confirming its anti-migratory and anti-invasive capabilities by inhibiting biomarkers linked to Wnt-signal-regulated epithelial-mesenchymal transition. Xiong et al discovered that rut effectively inhibits the proliferation of breast cancer cells and leads to cell-cycle arrest in MDA-MB-149 cells by upregulating miR-323-3p.[87] By reversing the rut-mediated miR-149-3p/S100A4 axis in breast cancer cells, apoptosis is promoted, autophagy is induced, and angiogenesis is inhibited, thereby preventing the malignant behavior of breast cancer. Lei et al developed a three-dimensional (3D) spheroid screening model based on morphological features and discovered that rut suppressed tumor growth by increasing cellular reactive oxygen species (ROS) levels while reducing the extracellular acidification rate (ECAR), oxygen consumption rate (OCR), and the ratios of NAD+/NADH and ATP/ADP in triple-negative breast cancer (TNBC) cells.[88] Lin et al found that rut significantly decreased tumor volume and weight, inhibiting the growth of prostate cancer cells by modulating Th1 polarization and maintaining immune balance in allogeneic TRAMP-C1 prostate cancer mice.[89] The effectiveness of cancer treatment faces a significant challenge from multidrug resistance (MDR).[90,91] Drug resistance due to ATP-binding cassette (ABC) transporters is a primary mechanism by which tumor cells develop multidrug resistance.[92,93] Zou et al were the first to report that rut enhanced the degradation of the ABCB1 protein by increasing the levels of MARCH8 protein, thereby counteracting ABCB1-mediated MDR.[94] In summary, their research lays the groundwork for the development of rut as a new anti-cancer drug. Glioblastoma is the most prevalent primary malignant neoplasm in the adult central nervous system. The remarkable migratory potential of tumor cells significantly contributes to the high recurrence rate and poor prognosis associated with glioblastoma.[95] Recent studies indicate that activating the aryl hydrocarbon receptor (AhR) may inhibit the migration of glioblastoma cells, underscoring the potential of AhR agonists as tumor inhibitors.[96] Liu et al found that rut, a naturally derived AhR agonist, significantly inhibits the migration of U87 human glioblastoma cells mainly through the AhR-IL24 pathway.[97] Globally, breast cancer is the most frequently diagnosed cancer among women.[98] Factors such as breast cancer subtype, tumor size, and stage significantly influence treatment responses and survival rates due to their heterogeneous characteristics. Esophageal cancer is recognized as an extremely aggressive malignancy. According to the World Health Organization's 2020 statistical analysis, esophageal cancer ranks as the sixth leading cause of cancer-related deaths and is the seventh most commonly diagnosed cancer globally. This highlights the urgent need for increased awareness and effective intervention strategies to combat this serious health threat.[99] As reported by Cokluk et al, rut exhibits cytotoxic and apoptotic effects in hormone-sensitive mammary tumor cells.[100] Research strongly demonstrates that rut significantly inhibits angiogenesis through the vascular endothelial growth factor receptor-mediated Akt/mTOR/p70S6K signaling pathway.[101] Wang et al established that rut plays a critical role in regulating the expression of key apoptotic markers, including p53, Bax, Bcl-2, caspase-9, and caspase-3. This regulation leads to the induction of apoptosis and a significant inhibition of cell growth in human esophageal squamous carcinoma CE81T/VGH cells, as demonstrated by both in vitro and in vivo experiments.[102]

Liver damage protection

The liver is a vital organ responsible for the production of plasma proteins, biliary secretion, the elimination of

xenobiotics, and the maintenance of glucose and lipid homeostasis.[103] Dysfunction in the regulation of liver functions frequently leads to liver diseases and their complications. The global prevalence of these diseases is increasing, resulting in higher rates of morbidity and mortality in advanced stages. This trend has become a significant public health concern and poses a substantial economic burden. Research has demonstrated that rut exerts a protective effect against acetaminophen-induced acute liver injury in murine models by inhibiting the expression of inflammatory cytokines associated with acetaminophen toxicity. This inhibition occurs through the suppression of NF-κB activation mediated by JNK1/2. Furthermore, rut pretreatment enhances Nrf2-mediated activation of the antioxidant enzymes GCLC, HO-1, and NQO1.[104] Through both in vitro and in vivo experiments, Wan et al demonstrated that rut exacerbates liver damage by upregulating CYP1A2 and pro-inflammatory factors.[105]

Other effects

Rut may exert an anti-psoriasis effect by modulating immune cells and reducing the expression of interleukin-6 (IL-6), interleukin-17A (IL-17A), and interleukin-23 (IL-23) in skin tissues.[106] Wang et al demonstrated that rutabaga significantly inhibited the growth of CE81T/VGH cells, promoted G2/M phase arrest, and induced apoptosis, thereby achieving antiproliferative effects.[102] Treatment with rutabaga alleviated nitroglycerin (NTG)-induced migraines in mice by reducing oxidative stress in both NTG-administered mice and H_2O_2-stimulated PC12 cells. This effect was mediated by the activation of the Nrf2 antioxidant system, which inhibits PGK1 activity through PTEN.[107] Elevated sucrose levels, commonly observed in Alzheimer's disease (AD), play a significant role in driving tau hyperphosphorylation, which in turn contributes to cognitive dysfunction and severe memory impairment. These findings suggest that rutabaga reduces the hyperphosphorylation of tau protein associated with AD and the cognitive deficits caused by a high-sucrose diet by inhibiting GSK-3β.[108] Migraine is a common neurovascular disorder that significantly impacts individuals' health and quality of life due to its widespread prevalence. This activation occurs through the inhibition of PGK1 activity via PTEN. The oxidative stress response that follows traumatic brain injury (TBI) triggers a cascade of secondary damage, leading to significant tissue injury and cell death.[109] Nuclear factor erythroid 2-related factor 2 (NRF2) plays a crucial role in defending the body against oxidative stress, effectively mitigating oxidative damage to neurons following TBI. Its protective functions make NRF2 a key player in promoting brain health and recovery after injury. Xu and colleagues found that rut alleviates oxidative stress-induced TBI and diminishes secondary damage through the PGK1/KEAP1/NRF2 signaling pathway, as demonstrated in both in vivo and in vitro studies.[110] Globally, obesity has reached epidemic proportions, contributing to an annual mortality rate of at least 2.8 million individuals due to overweight or obesity. Rut promotes adipose thermogenesis and provides protection against high-fat diet (HFD)-induced obesity through the AMPK/PGC-1α pathway.[58] Chronic obstructive pulmonary disease (COPD) is a debilitating inflammatory lung condition characterized by limited airflow and significant breathing difficulties. In a compelling study, Ji et al demonstrated that rut offers protective effects against COPD induced by cigarette smoke in rats, highlighting its potential as a promising therapeutic intervention.[111] Osteoporosis is a systemic disease closely linked to the aging process, marked by a significant reduction in bone mass and the deterioration of bone microstructure. This debilitating condition dramatically increases the risk of fractures, leaving individuals vulnerable to debilitating injuries that can profoundly impact their quality of life. Understanding and addressing osteoporosis is crucial for maintaining healthy bones and preventing serious complications as we age. It poses a significant global healthcare challenge, underscoring the need for effective preventive strategies. Ali et al demonstrated that apigenin and rut enhance osteoblastic differentiation and bone formation while alleviating age-related effects on human bone marrow stem cells (hBMSCs).[112] Psoriasis is a chronic, immune-mediated inflammatory skin condition. Li et al discovered that rut inhibits imiquimod-induced psoriasis-like dermatitis by suppressing the NF-κB and TLR7 pathways in mice.[113] Wan et al conducted both in vivo and in vitro experiments confirming that rut worsens acetaminophen-induced acute liver damage by increasing the levels of CYP1A2 and pro-inflammatory factors.[105] This dual effect's finding indicates the importance of carefully considering the combination dose of rut with acetaminophen in drug design and preclinical trials. AD is a profoundly devastating and irreversible neurological disorder, and we are facing a critical shortage of effective small-molecule treatments to combat this challenging condition. However, recent research highlights a promising avenue for treatment: phosphodiesterase 5 (PDE5) inhibitors. Notably, rutabaga has been shown to exhibit significant inhibitory activity against PDE5, positioning it as a potential breakthrough in the fight against Alzheimer's disease.[114]

Pharmacokinetics

Mechanism of absorption

There are several routes for administering rut, including oral, injection, and transdermal methods. Each route affects the rate and extent of absorption differently. Oral administration is the most common method; however, due to its poor water solubility, its dissolution and absorption in the gastrointestinal tract can be challenging. Research indicates that its intestinal absorption follows a specific rate process. For instance, in a rat intestinal absorption model, various doses of rut were administered using 4% Tween 80 as the solvent. The results showed that absorption increased with the dose, and the absorption

rate constant remained relatively stable, suggesting that the process is primarily driven by passive diffusion. Upon oral administration, the drug faces a series of formidable challenges. It must navigate the harsh acidic and basic environments of the gastrointestinal tract, contend with the action of digestive enzymes, and penetrate the intestinal mucosal barrier. These obstacles significantly reduce its bioavailability, underscoring the complexities involved in effective drug absorption.[115] Drug administration via injection, including intravenous and intramuscular routes, allows for rapid entry of drugs into the bloodstream, bypassing the first-pass metabolism of the gastrointestinal tract and facilitating a swift onset of action. For instance, in a canine intravenous injection study, the blood concentration of rut reaches its peak within a short time, demonstrating a strong linear correlation between the dose administered and the resulting blood concentration within a specific dosage range.[116] However, injection methods have higher preparation requirements, necessitating the assurance of sterility and the absence of pyrogens in the drug. Transdermal administration offers the advantages of bypassing the first-pass effect in the liver and maintaining a relatively stable blood concentration. Several studies have investigated the transdermal formulation of rut and found that, with appropriate osmotic enhancers and dosage forms, the drug can be delivered slowly and continuously into the body through the skin. Wang et al noted that the rate of percutaneous absorption is relatively slow, significantly influenced by the thickness and integrity of the stratum corneum of the skin, as well as the drug dosage form.[41]

Characteristics of distribution

The distribution of rut across various tissues and organs exhibits a distinct pattern following its entry into the body. Studies have demonstrated that rut is present in the liver, kidneys, heart, brain, and other organs, with varying concentrations across different tissues. In a tissue distribution study conducted after the oral administration of Xianglian pills in mice, UPLC-MS/MS analysis revealed a high distribution ratio of rut in the colon. This finding may be associated with the therapeutic effects of rut on intestinal diseases. The relatively high concentration of rut in target tissues enhances its potential pharmacological effects.[117] Rut can be distributed to cardiomyocytes, vascular endothelial cells, and other tissues, where it regulates intracellular signaling pathways, playing a crucial role in vasodilation and myocardial protection. Its distribution characteristics establish a foundational basis for the targeted application of pharmacological effects.

Metabolic pathways

Pharmacokinetic studies on the traditional Chinese medicine *Cornus officinalis* are quite extensive, primarily focusing on its active components, such as *Cornus* alkaloids and rut. Researchers at the Institute of Applied Chemistry in Taiwan developed a high-performance liquid chromatographic method to measure the concentration of rut in the plasma of rats after intravenous injection.[118] The results showed that the pharmacokinetics of rut in rats followed a two-compartment model. The clearance half-life (t1/2) was measured at 29.29 ± 4.25 minutes, and the area under the drug-time curve (AUC) was found to be 32.93 ± 3.99 μg min mL^{-1}. Lee et al have developed a highly sensitive and effective method for the detection and characterization of the rut metabolites in Sprague-Dawley (SD) rats. A total of 17 metabolites were detected and identified in rat plasma, including eight novel metabolites (specifically, dihydroxylation and sulfate conjugation products of rut, designated as M10-M17), along with the parent drug itself.[119] The identified metabolites included three phase I and 12 phase II metabolites. Hydroxylation, sulfate conjugation, and glucuronidation are the primary metabolic pathways for rut in rat plasma. Figure 3 presents a thorough investigation of the phase I and II metabolites of rut in freshly isolated hepatocytes from male SD rats. Utilizing advanced liquid chromatography-tandem mass spectrometry, we meticulously characterized the individual metabolites. Remarkably, following a two-hour incubation of rut with these freshly isolated hepatocytes, we successfully identified five primary phase I metabolites, underscoring the metabolic complexity and significance of rut in hepatic processes. Three glucuronide conjugates and four sulfate conjugates were also identified. Since most metabolites observed in vivo were detected, freshly isolated hepatocytes may be useful for identifying specific metabolites produced from drug candidates while reducing the number of experimental animals needed.[120] Song et al established a diabetic rat model by administering a high-fat diet in conjunction with a low dose of streptozotocin.[121] The pharmacokinetic findings from the administration of metformin, whether combined with rut or not, over a period of 42 days, clearly demonstrate that the addition of rut does not alter metformin's systemic exposure or its renal distribution. This suggests that metformin's efficacy remains uncompromised, reinforcing its reliability as a treatment option. However, it did increase the concentration of metformin in the liver. Additionally, rut enhanced the uptake of metformin by hepatocytes mediated by the Oct1 transporter by upregulating Oct1 expression in the liver. Cheng et al employed cutting-edge ultra-high-performance liquid chromatography combined with quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS) to effectively identify the key chemical constituents in the aqueous extract of Cornus officinalis. Their innovative approach underscores the potential of this technique in advancing our understanding of the complex phytochemistry of this plant.[122] They conducted a thorough analysis of the aqueous extract's in vivo composition in rats after gavage administration. The study identified and hypothesized the presence of hypaconitine from *Cornus officinalis* and its metabolites in the plasma, urine, and feces of rats that received the aqueous extract via gavage. Lee et al

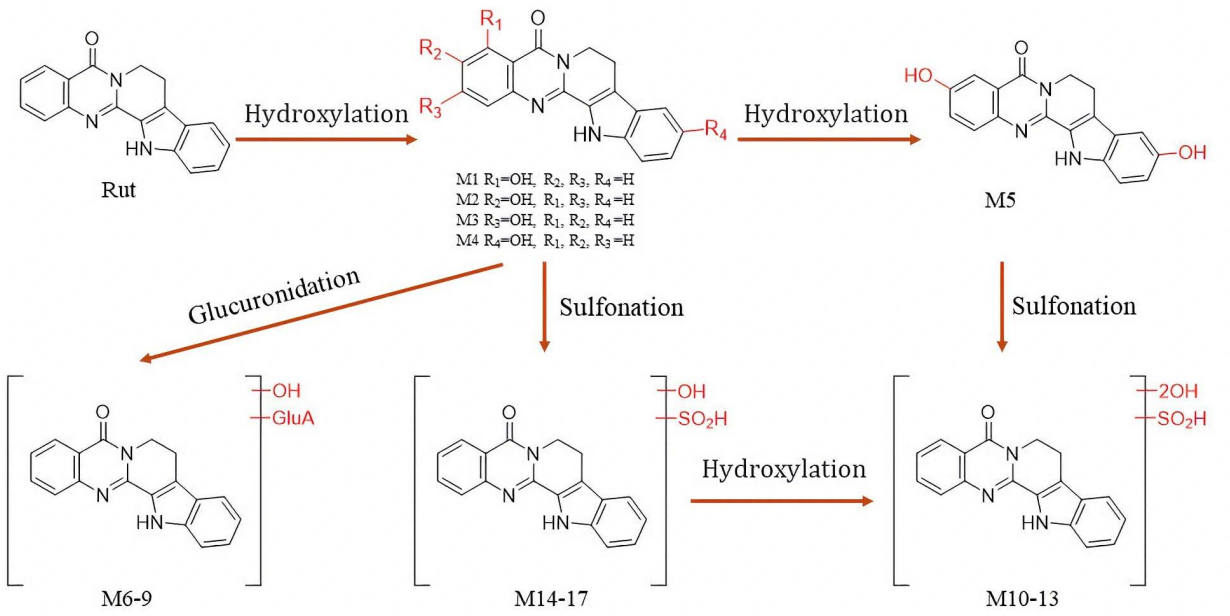

Figure 3. Metabolic pathways and metabolites of rutaecarpine *in vivo*

conducted an in-depth study on the interaction between rut and acetaminophen (APAP) in male Sprague-Dawley rats, revealing significant insights into their effects on each other.[123] The area under the plasma concentration-time curve over one hour demonstrated a significant reduction when 25 mg/kg of APAP and 80 mg/kg of rut were administered intravenously together, compared to the administration of rut alone. This finding highlights the impactful interaction between these compounds. When rats were administered oral doses of 40 mg/kg and 80 mg/kg of rut over a three-day period, there was a striking reduction in the maximum concentration (Cmax) and AUC for the acetaminophen-sulfate conjugate. Specifically, these values plummeted to just 56.4% and 61.7%, respectively, compared to the carrier control group. This significant decrease underscores the potent effects of rut on acetaminophen metabolism. These findings strongly suggest that rut has the potential to significantly alter the pharmacokinetic parameters of acetaminophen (APAP) in rats. In their study, Estari et al identified the minimum duration required for the oral administration of rut to manifest its effects on the pharmacokinetics (PK) of caffeine, specifically in a controlled group of 15 male Sprague-Dawley rats.[124] Pharmacokinetic parameters for caffeine and its metabolites were analyzed for both the control and rut groups using WinNonlin®. The findings revealed that administering a 100 mg/kg dose of rut just 3 hours prior to caffeine remarkably reduced both the systemic exposure and mean residence time of caffeine and its metabolites. This significant decrease underscores the potential impact of rut on caffeine metabolism. This reduction was attributed to a decrease in caffeine's bioavailability (up to 75%) and an increase in clearance. Systemic exposure to caffeine and its metabolites is less prominent when caffeine is administered intravenously compared to oral administration. Although plasma levels of rut are undetectable (less than 10 ng/mL), it still induces hepatic CYP1A2 activity. Pharmacokinetic research shows that rut is poorly absorbed in vivo, necessitating further investigation into strategies to enhance its absorption.

Process of excretion

Rut and its metabolites are predominantly expelled by the kidneys and effectively eliminated through urine. Following intravenous administration, the blood concentration of the drug decreases rapidly during the initial phase, quickly transitioning into the renal excretion stage, which is characterized by a high excretion rate that gradually stabilizes. Additionally, some metabolites can be excreted into the intestine via bile and subsequently eliminated in feces.[125] During the drug development process, it is essential to study excretion mechanisms and rates, as this information is critical for assessing the residual risk of the drug in the body. If the excretion rate is too slow, the drug or its metabolites may accumulate, potentially leading to toxic reactions. By understanding the characteristics of excretion, we can effectively design the drug dosing regimen to prevent accumulation and ensure medication safety. For example, in patients with liver and kidney insufficiency, the dosage should be adjusted based on the excretion characteristics of rut to prevent adverse reactions, such as liver and kidney injury, caused by excessive drug accumulation due to impaired excretory function.

Formulation design

Rut has demonstrated significant activity in models related to cardiovascular protection, anti-tumor effects, inflammation, and liver injury, highlighting its potential for promising applications. However, due to the active

compound's poor oral bioavailability, it is crucial to employ formulation technologies to enhance its bioavailability for the development of an effective drug candidate for treating cardiovascular diseases. Given Rut's limited aqueous solubility, slow dissolution rate, and low bioavailability, its solubility and bioavailability can be improved through rational formulation strategies, including nano-formulations, encapsulations, patches, and creams. Relevant dosage form studies are summarized in Table 2. These formulation approaches offer distinct advantages and limitations, such as enhancing bioavailability and therapeutic efficacy while addressing challenges related to production complexity, cost, and patient compliance. The selection of the dosage form should be tailored to specific clinical needs and manufacturing capabilities.

Perspectives and future directions

Evodia rutaecarpa is a well-established herbal medicine recognized for its diverse bioactivities and therapeutic benefits. It has been used clinically as a complementary therapy for treating abdominal pain, bloating, vomiting, and diarrhea.[1] Rut, an indole alkaloid derived from *Evodia rutaecarpa*, demonstrates significant pharmacological activities. Cardiovascular diseases (CVDs) are the foremost cause of death around the world, emphasizing the urgent need for awareness and preventative measures. The consistently high levels of morbidity, mortality, and disability underscore the urgent need for further investigation into preventive strategies and alternative therapeutic approaches.[132] Rut plays a beneficial role in CVDs, including hypertension, diabetes, atherosclerosis, and hyperlipidemia. The article published in 2019[6] merely provided some references on the cardiovascular protective effect and mechanism of rut, and there were deficiencies in terms of research depth, scope, clinical transformation, and research design. In this paper, we summarize the mechanisms by which rut exerts its effects against cardiovascular diseases, both in vitro and in vivo, and we confirm the promising efficacy of rut in the treatment of these conditions. Rut exhibits a diverse range of impressive functions, including antibacterial, antiviral, anti-inflammatory, antioxidant, neuroprotective, and cardioprotective properties. These characteristics hold the potential to significantly advance the future of human medicine. However, critical gaps remain in the pharmacological assessment of rut, underscoring the urgent need for further research into its in vivo activity. Addressing these gaps could unlock new therapeutic possibilities and enhance our understanding of rut's full potential in medical applications.

The metabolism of rut in the body is complex and involves various enzymes, particularly the cytochrome P450 (CYP450) enzymes, which play a crucial role in its metabolic activation. This complexity may contribute to drug-drug interactions and potential toxic effects when rut is used in combination with other medications. Research indicates that rut's reduced bioavailability is due to its low solubility, the hepatic first-pass effect, and phase II metabolic reactions. These factors can negatively impact absorption and diminish the drug's efficacy in the human body. As a promising lead compound, addressing the solubility and bioavailability of rut is critical.[133] Strategies to address low drug solubility are continually evolving. These strategies encompass the formation and selection of salts, the application of amorphous formulations, and the creation of self-emulsifying systems. Furthermore, there is a growing exploration of lipid-based formulations, nanoparticle systems, and innovative materials, all of which promise to enhance effectiveness and optimize performance in various applications. There are also novel applications of existing materials, advancements in solubilization techniques, and improved methods for screening tissue absorption. Finally, optimizing pharmaceutical processes plays a crucial role in enhancing drug solubility. The skin permeability of rut was significantly enhanced by incorporating an oil-in-water microemulsion as a carrier, resulting in increased skin flux. Additionally, the bioavailability of rut was improved through the formulation preparation.[134] The water solubility of rut was increased by approximately 550-fold through the formation of an inclusion complex with urea.[135] Rut is classified as a BCS Class II drug in the Biopharmaceutics Classification System, which means its absorption depends on its solubility. Key factors like particle size, dissolution rate, and the choice of excipients play a crucial role in determining pharmacokinetics. To maximize the bioavailability of BCS Class II drugs, it is vital to enhance both their solubility and that of the formulation itself. By doing so, we can significantly improve oral absorption and ensure that these medications are more effective for patients. Common strategies employed to achieve this include the development of nanoparticles, phospholipid complexes, and other advanced formulations. Current investigations primarily focus on

Table 2. Research on dosage forms of rut

Formulation	Dosage form advantages	Reference
nanoparticle	Preparation into lipid cubic liquid crystal nanoparticles with high encapsulation rate and higher efficacy than APIs	126
Nanosuspension Paste	Effective in increasing transdermal drug penetration	127
inclusion complex	Improved water solubility and bioavailability	128
Nanosuspension Gel	Promote transdermal absorption rate and increase permeability	129
balm	Stable and convenient properties	130
transdermal patch	Good adhesion and transdermal permeability	131

the differences in bioavailability when comparing the formulation to the original drug, as well as the evaluation of the formulation's quality. In drug design, rut serves as the lead structure, which is modified using strategies such as skeleton modification, molecular hybridization, and skeleton hybridization, along with a quality evaluation of the formulation. Additionally, rut is utilized as another lead structure for drug design, undergoing modifications and optimizations through backbone modification, molecular hybridization, backbone leaping strategies, and enhancements in its physicochemical properties and material encapsulation techniques.

Conclusion

Evodiae fructus is a traditional Chinese herbal medicine, and rut, one of its key active ingredients, is currently under investigation in drug formulation technology and remains in the developmental stage. The studies presented in this review compellingly illustrate the significant potential of rut in drug development. Thorough and detailed research into the pharmacological effects and metabolism of rut is essential to position it as a leading candidate for clinical applications.

Authors' Contribution

Conceptualization: Sen Wang.
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Project administration: Chaohuai Yang.
Supervision: Shuiping Ou.
Writing–original draft: Chaohuai Yang, Fang Mei, Peng Li.
Writing–review & editing: Chaohuai Yang, Fang Mei, Peng Li.

Competing Interests

All authors affirm that they possess no conflicts of interest, ensuring the integrity and impartiality of this work.

Data Availability Statement

No primary research results, software, or code were included, and no new data were generated or analyzed as part of this review.

Ethical Approval

Not applicable.

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