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From *Rubus idaeus* to Oncology: A Critical Review of Raspberry Ketone as a Plant-Derived Bioactive Compound in Cancer Prevention, Redox Regulation, and Molecular Therapeutic Pathways

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ABSTRACT

Raspberry ketone, a bioactive phenolic compound derived from *Rubus idaeus*, has gained attention for its potential role in cancer prevention and supportive oncology. Preclinical studies demonstrate that it exerts antioxidant, anti-inflammatory, and pro-apoptotic effects, modulating redox balance, cell cycle progression, and inflammatory signaling. In vitro studies show inhibition of proliferation and induction of apoptosis across multiple cancer cell lines, while in vivo models report reduced tumor growth, enhanced antioxidant enzyme activity, and improved survival outcomes. Despite these promising findings, translation into clinical use is limited by low oral bioavailability, rapid metabolism, and lack of standardized dosing. Safety data on long-term high-dose exposure remain insufficient, highlighting the need for rigorous pharmacokinetic and toxicological studies. Future research should focus on novel delivery systems, combination therapies with conventional treatments, and well-designed clinical trials to establish efficacy and safety. Understanding the molecular mechanisms underlying raspberry ketone's anticancer effects can support its development as a plant-derived adjunct in cancer prevention and integrative oncology.

Keywords: Raspberry Ketone; *Rubus Idaeus*; Oncology; Cancer Prevention; Redox Regulation; Oxidative Stress; Apoptosis; Phytochemicals; Molecular Pathways

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INTRODUCTION

Raspberry ketone (4-(4-hydroxyphenyl)-2-butanone) is a naturally occurring aromatic compound predominantly found in red raspberries (*Rubus idaeus*) and is widely utilized in the food, fragrance, and cosmetic industries due to its distinctive aroma and flavor [1,2]. Beyond these applications, raspberry ketone has attracted scientific interest for its potential biological and therapeutic properties, including antioxidant, anti-inflammatory, and cytoprotective effects [3,4]. Such properties are particularly relevant to oncology, as oxidative stress, chronic inflammation, and impaired apoptosis are critical contributors to cancer initiation, progression, and metastasis [5,6].

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) and cellular antioxidant defenses, promotes genomic instability, DNA damage, and tumorigenesis [7,8]. Raspberry ketone may mitigate these effects by scavenging free radicals, enhancing endogenous antioxidant enzymes such as superoxide dismutase and catalase, and regulating redox-sensitive signaling pathways [9,10]. In addition, raspberry ketone can modulate apoptosis by upregulating pro-apoptotic proteins (Bax) and downregulating anti-apoptotic proteins (Bcl-2), as well as inducing cell cycle arrest at critical checkpoints to inhibit uncontrolled proliferation [11,12].

Preclinical studies have further demonstrated that raspberry ketone influences multiple molecular pathways, including NF-κB and MAPK signaling, while reducing pro-inflammatory cytokines such as TNF-α and IL-6 [13,14]. These mechanisms collectively suggest a potential role for raspberry ketone as a chemopreventive or adjunctive agent in cancer management. Nevertheless, clinical evidence is currently limited, and challenges such as low oral bioavailability, rapid metabolism, and the absence of standardized dosing hinder direct therapeutic translation [15,16].

In summary, understanding the molecular mechanisms underlying raspberry ketone's redox regulation, anti-inflammatory effects, and apoptosis modulation provides a foundation for future research into its potential as a plant-derived adjunct in cancer prevention and supportive oncology [17,18].

Phytochemical Properties of Raspberry Ketone

Raspberry ketone (4-(4-hydroxyphenyl)-2-butanone) is a phenolic

aromatic ketone predominantly found in red raspberries (*Rubus idaeus*) and contributes to the fruit's characteristic aroma and flavor [19,20]. Due to its low natural abundance, synthetic and biotechnological production methods have been developed to meet commercial and research demands [21,22]. Recent advances in microbial biosynthesis provide a sustainable approach for large-scale production, enabling more consistent quality and higher yields [23].

The chemical structure of raspberry ketone, with a hydroxyphenyl group linked to a butanone backbone, underlies its potent antioxidant and bioactive properties [24]. These include scavenging of free radicals, modulation of cellular redox balance, and regulation of pro-inflammatory mediators such as TNF-α, IL-6, and COX-2 [25,26]. The phenolic nature of raspberry ketone also allows it to interact with signaling pathways related to oxidative stress and inflammation, which are crucial in preventing DNA damage and tumor initiation [27].

Despite promising bioactivities, the oral bioavailability of raspberry ketone is limited due to rapid hepatic metabolism and low systemic absorption [28]. Formulation strategies such as encapsulation in nanoparticles or liposomes are being explored to enhance bioavailability, improve tissue distribution, and enable targeted delivery [29,30]. These approaches aim to maximize the therapeutic potential of raspberry ketone while maintaining safety [Table 1].

Table 1: Phytochemical Properties and Extraction Methods of Raspberry Ketone.

Property	Details
Chemical Structure	4-(4-hydroxyphenyl)-2-butanone, aromatic ketone
Natural Sources	Red raspberry (*Rubus idaeus*)
Synthetic Production	Microbial biosynthesis, chemical synthesis
Extraction Methods	Solvent extraction, steam distillation, biotechnological methods
Bioavailability	Low oral bioavailability; rapid metabolism in liver

Biological Activities and Mechanisms in Cancer Prevention

Raspberry ketone exhibits multiple biological activities relevant to cancer prevention, mainly through antioxidant, anti-inflammatory, and pro-apoptotic effects [31,32]. Its antioxidant activity enables scavenging of reactive oxygen species (ROS), thereby preventing oxidative DNA damage, protein modification, and lipid peroxidation—critical processes in tumor initiation [33,34].

Raspberry ketone also modulates apoptosis, the programmed cell death pathway essential for eliminating damaged or pre-cancerous cells. It promotes apoptosis by upregulating pro-apoptotic proteins (Bax) and downregulating anti-apoptotic proteins (Bcl-2), activating mitochondrial-mediated pathways and halting tumor progression [35,36].

In addition, raspberry ketone can induce cell cycle arrest at the G1/S or G2/M checkpoints, inhibiting the replication of damaged DNA and preventing uncontrolled proliferation [37,38]. Anti-inflammatory effects are another critical mechanism: it reduces levels of pro-inflammatory cytokines such as TNF-α, IL-6, and COX-2, which are closely linked to tumor promotion, angiogenesis, and metastasis [39,40].

Preclinical studies, including both in vitro and in vivo models, have provided evidence of raspberry ketone's anticancer potential. Cell-based studies across breast, colon, and liver cancer lines have demonstrated inhibition of cell growth, induction of apoptosis, and suppression of metastatic behavior [41,42]. Complementary animal studies have shown reduced tumor size, improved antioxidant enzyme activity, and enhanced survival outcomes [43,44]. Despite promising preclinical results, clinical evidence remains limited, and optimization of bioavailability and dosing is required before translational applications [45,46] [Table 2].

Table 2: Biological Activities and Mechanisms of Raspberry Ketone in Cancer Prevention.

Mechanism	Cellular / Molecular Effect
Antioxidant Activity	Scavenges ROS, enhances antioxidant enzymes (SOD, CAT), prevents DNA damage
Apoptosis Induction	Upregulates Bax, downregulates Bcl-2, activates mitochondrial apoptosis
Cell Cycle Arrest	Arrests cell cycle at G1/S or G2/M checkpoints, inhibits proliferation
Anti-inflammatory Effects	Reduces TNF-α, IL-6, COX-2; inhibits NF-κB and MAPK signaling
Antiproliferative / Antimetastatic	Inhibits growth and migration of cancer cells in breast, colon, liver lines
In Vivo Tumor Suppression	Reduces tumor size, enhances antioxidant defense, improves survival in animal models

Preclinical Evidence: In Vitro and In Vivo Studies

Preclinical investigations provide crucial insight into the anticancer potential of raspberry ketone. In vitro studies have demonstrated that raspberry ketone inhibits cell proliferation, induces apoptosis, and reduces migration and invasion across multiple cancer cell lines, including breast, colon, and liver cancer models [47,48]. Mechanistically, these effects are mediated through modulation of NF-κB, MAPK, and PI3K/Akt signaling pathways, which are central to cell survival, inflammation, and metastasis [49,50].

In vivo studies in animal models further support the chemopreventive potential of raspberry ketone. Mouse models of breast and skin cancer treated with raspberry ketone have shown reduced tumor volume, enhanced antioxidant enzyme activity, and improved survival outcomes compared to controls [51,52]. Additionally, raspberry ketone exhibits protective effects against chemically induced organ toxicity, highlighting its cytoprotective and systemic antioxidant properties [53,54].

Despite these encouraging results, the preclinical evidence is primarily limited to small-scale studies with variable dosing regimens and administration routes. Standardized experimental models, larger sample sizes, and long-term studies are needed to validate these findings and establish safe and effective dosing parameters for translational applications [55,56] [Table 3].

Table 3: Summary of Preclinical Studies on Raspberry Ketone's Anticancer Effects.

Study Type	Cancer Model / Cell Line	Mechanisms Investigated	Major Findings
In Vitro	Breast (MCF-7), Colon (HT-29), Liver (HepG2)	Apoptosis, cell cycle arrest, NF-κB, MAPK	Reduced proliferation, induced apoptosis, inhibited migration
In Vivo	Breast cancer (BALB/c mice), Skin cancer (C57BL/6 mice)	Tumor growth, antioxidant enzymes, survival	Decreased tumor size, improved antioxidant status, increased survival
In Vivo	Liver and lung toxicity models	ROS modulation, anti-inflammatory pathways	Protected organs from chemical-induced toxicity

CHALLENGES AND FUTURE DIRECTIONS

Despite the promising preclinical evidence, the translation of raspberry ketone into clinical oncology applications faces several challenges. One of the major limitations is its poor oral bioavailability, which restricts systemic exposure and reduces its therapeutic potential [57,58]. Rapid metabolism in the liver further limits the concentration of active compounds reaching target tissues, necessitating the development of advanced delivery systems such as nanoparticles, liposomes, or prodrugs to enhance bioavailability and efficacy [59,60].

Safety and toxicity are another area of concern. While raspberry ketone is generally recognized as safe in dietary amounts, the long-term effects of high-dose supplementation remain unclear, and potential adverse effects on liver or kidney function have not been comprehensively studied [61,62]. Establishing safe and effective dose ranges is essential for both preventive and therapeutic applications.

Moreover, the current preclinical evidence is largely limited by small sample sizes, lack of standardized models, and variable dosing regimens. In vitro and in vivo studies often use different administration routes, concentrations, and exposure durations, making it difficult to compare results and draw conclusive translational insights [63,64]. Robust clinical trials are therefore critical to validate efficacy, determine pharmacokinetics in humans, and assess long-term safety.

Future research should also explore synergistic effects with conventional therapies, including chemotherapy, radiotherapy, and immunotherapy. Combining raspberry ketone with standard treatments may enhance therapeutic outcomes while potentially reducing toxicity [65,66]. Additionally, elucidating the molecular mechanisms underlying its anticancer effects, including redox regulation, apoptosis, and inflammation, can guide the rational design of adjunctive strategies in oncology [Table 4].

Table 4: Key Challenges and Proposed Solutions for Clinical Translation of Raspberry Ketone.

Challenge	Description	Proposed Solution
Bioavailability	Low absorption and rapid hepatic metabolism	Nanoparticle or liposomal formulations, prodrug strategies
Safety Concerns	Long-term toxicity unknown at high doses	Conduct comprehensive toxicity and dose-finding studies
Preclinical Evidence Gaps	Small sample sizes, variable models and dosing	Standardize experimental models, larger preclinical studies
Clinical Translation	Lack of human trials	Design randomized controlled trials to assess efficacy and safety
Combination Therapy Potential	Unknown synergistic effects with standard therapies	Investigate combination with chemotherapy, radiotherapy, and immunotherapy

CONCLUSION

Raspberry ketone, a bioactive compound derived from *Rubus idaeus*, demonstrates multifaceted anticancer potential through its antioxidant, anti-inflammatory, and pro-apoptotic effects. Preclinical studies indicate that it can modulate redox balance, regulate apoptosis, induce cell cycle arrest, and suppress inflammatory signaling, collectively contributing to reduced tumor proliferation and metastasis.

Despite promising in vitro and in vivo evidence, the translation of raspberry ketone into clinical oncology is limited by poor oral bioavailability, rapid metabolism, and insufficient standardized dosing strategies. Moreover, long-term safety and toxicity data at higher doses are still lacking, emphasizing the need for rigorous pharmacokinetic and toxicological studies.

Future research should focus on novel delivery systems, including nanoparticles, liposomes, and other formulation strategies, to enhance bioavailability and improve tissue targeting. Investigation of synergistic effects with conventional therapies, such as chemotherapy, radiotherapy, or immunotherapy, may further improve therapeutic outcomes while reducing systemic toxicity.

Overall, raspberry ketone holds promise as a plant-derived adjunct in cancer prevention and supportive oncology. Well-designed preclinical and clinical trials, alongside detailed mechanistic studies, are necessary to validate its efficacy and safety. As research progresses, raspberry ketone may become a valuable integrative approach in modern cancer care, bridging nutraceutical research and translational oncology.

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