Anticancer Effects of Carvacrol in In Vitro and In Vivo Models: A Comprehensive Review

Fahad Khan 1, Pratibha Pandey 1,*, Ramish Maqsood 1, Tarun Kumar Upadhyay 2

1 Department of Biotechnology, Noida Institute of Engineering & Technology, 19, Knowledge Park-II, Institutional Area, Greater Noida 201306, India; fahadintegralian@gmail.com (F.K.); shukla.pratibha1985@gmail.com (P.P.); ramish@niet.co.in (R.M.);
2 Animal Cell Culture and Immuno-Biochemistry Lab, Department of Biotechnology, Parul Institute of Applied Sciences and Centre of Research for Development, Parul University, Vadodara 391760, India; tarun_bioinfo@yahoo.co.in (T.K.U.);
* Correspondence: shukla.pratibha1985@gmail.com (P.P.);

Scopus Author ID 54985258500

Received: 8.04.2022; Accepted: 18.05.2022; Published: 10.07.2022

Abstract: Carvacrol is an active phenolic monoterpenoid with enormous anticancerous potential against numerous carcinomas, including prostate, gall bladder, and cervical, and has gained wider recognition in chemotherapeutics. Therefore, this review targeted to study and summarize various in vitro and in vivo research studies associated with the anticancerous potential of carvacrol with its associated mechanisms in several carcinomas. Carvacrol-treated cancer cells have exhibited significant apoptotic induction, cell cycle arrest, cytotoxicity, antimetastatic activity, and different antiproliferative effects via targeting numerous signaling pathways, including MAPKs, Notch PI3K, mTOR, and AKT. In vitro, carvacrol appears to be a highly potent phytoactive compound against several carcinomas. However, more in vivo research with better methodology are still needed to elucidate safe and standard dose, determine their toxic effects and elaborate its exact mode of action to develop a potential therapeutic approach for cancer management.

Keywords: carvacrol; monoterpen; bioactive compound; anticancer; therapeutic potential

© 2022 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

According to WHO (World Health Organization, 2020), it has been estimated that one in five people globally faces a diagnosis of a few malignant neoplasms, which is forecast to increase exponentially by 2040 [1]. Cancer is a major worldwide public health issue and has been among the four crucial reasons for premature death in many countries, leading to 8.8 million deaths annually as per the 2019 report of the National Cancer Institute. Several antineoplastic agents have improved the patient survival rate but have posed various side effects and worsened the quality of life of these patients [2-5]. Thus, more research should be focused on exploiting the therapeutic potential of phytocompounds that can further be utilized to develop a more potent and effective treatment against cancer with limited toxic side effects. However, several medicinal plants with potent pharmacological properties have been discovered [6]. However, nature still grips several bioactive compounds without sufficient reports, specifically in cancer biology [7, 8]. Secondary plant metabolites have made major contributions to cancer therapeutics via targeting major signaling pathways, such as vinca alkaloids, perillyl alcohol, limonene (monoterpenes), and paclitaxel [9-11]. In this context, we have summarized our review covering numerous in vivo and in vitro anticancerous studies...
reporting the anticancerous potential of carvacrol (5-isopropyl-2-methylphenol) with its associated mode of action. Carvacrol (monoterpenoid phenol) is one of the main components found in essential oils obtained from various plant species such as *Origanum vulgare*, *Lippia gracilis*, and *Thymus vulgaris* [12-14], that have previously been reported to display medicinal benefits against several diseases, such as cancer [15, 16] (Figure 1).

![Diagram of Carvacrol's efficacy in various types of carcinoma](image)

**Figure 1.** *In vitro* and *in vivo* efficacies of carvacrol in various types of carcinoma.

Carvacrol (C۱۰H۱۴O) is a liquid phenolic monoterpenoid, 2-methyl-5-(1-methylethyl)phenol, present in the essential oil of *Origanum vulgare* (oregano), *Thymus vulgaris* (thyme), *Lepidium flavum* (pepperwort), *Citrus aurantium* var. bergamia Loisel (wild bergamot), and several other plants [17, 18]. Commercial carvacrol is synthesized via various biotechnological and chemical methods. It has been recognized as 5-isopropyl-2-methyl phenol by IUPAC (the International Union of Pure and Applied Chemistry) and has a density of 0.976 g/ml at 25 °C. It is lipophilic and insoluble in water but is highly soluble in diethyl ether, ethanol, and acetone [19].

Carvacrol (FDA authorized) has also been included in the list of chemical flavorings used in alcoholic beverages, baked goods, chewing gum, condiment relish, frozen dairy, gelatin pudding, nonalcoholic beverages, and soft candies, according to the Council of Europe. Carvacrol is used as a preservative in various foods, including rice, grape tomatoes, grapes, apple juice, semi-skimmed milk, fresh-cut kiwifruit, and honeydew melon. It has been reported to be strongly effective in reducing the growth of food spoilage and pathogenic bacteria when used alone or in conjunction with other naturally occurring organic molecules. Carvacrol has also been found to be an effective antioxidant in poultry feed, lowering lipid oxidation and so boosting meat nutritional quality. Feed supplementation could be a straightforward and convenient way to get lipid-soluble antioxidants into phospholipid membrane tissues, where they can efficiently suppress oxidative processes in specific places. Concerns about the safety of synthetic antioxidants like butylated hydroxytoluene and butylated hydroxyanisole have also prompted increased research into plant ingredients like carvacrol.
As recently reported by numerous researchers, carvacrol exhibited a wider range of biological activities, such as antiviral [20, 21], antibacterial and antifungal [22-24], and anticarcinogenic [25, 26], antioxidant properties [27, 28]. Due to antimicrobial and flavoring activities, carvacrol has also been utilized as a natural food preservative in the food industry [29, 30].

In addition, carvacrol has also presented potent anti-inflammatory and antioxidant potential via reducing inflammation and increasing the non-enzymatic and enzymatic antioxidants in the tumor environment [31, 32]. Hence, this review aims to summarize all the best possible studies reported for carvacrol's antiproliferative and anticancerous potential to provide strong guidance for future carvacrol-based studies.

2. Anticancerous potential of carvacrol against different cancer cell lines

Carvacrol showed significant growth inhibitory potential in the A549 cell line (lung cancer cells) at respective doses of 500 and 1,000 µM with induction of early apoptotic characteristics [33] via inhibition of AXL (tyrosine kinase receptor) expression and enhanced MDA (malondialdehyde) and 8-OHdG (hydroxy-2′-deoxyguanosine) expression levels (8-OHdG) [34, 35]. Carvacrol has also displayed potent antitumor effects in HepG2 cells (hepatocarcinoma) by inducing cell death via the mitochondrial-mediated pathway, accompanied by Bel-2 inhibition and caspase-3 activation in a dose-dependent manner [36]. Similarly, Melu’sovit et al. (2014) have also demonstrated the apoptotic efficacy of carvacrol (650 μM) via growth arrest in G1 and S phases [37]. Caco-2 cancer cells have also exhibited decreased cell viability and increased early apoptotic cells after carvacrol treatment (115 μM) [38]. Carvacrol also has displayed inhibition of HCT116, HT-29 cell proliferation, and reduced metalloproteinases, Bel-2, p-Akt, p-ERK, and cyclin B1 levels leading to cell cycle arrest at the G2/M phase [39-41].

![Figure 2. The mechanism associated with the anticancer mode of action of carvacrol.](https://biointerfaceresearch.com/)

https://doi.org/10.33263/BRIAC133.290
Numerous research reports have strongly depicted the cytotoxic and pro-apoptotic efficacy of carvacrol against various cancer cells in a time and dose-dependent manner, with significant effects on cell invasion via reduced matrix metalloprotease 2 and 9 expression levels in treated cells [39]. A plethora of cancerous cells, including Hep-2 human larynx carcinoma cells, mouse B16 melanoma, leiomyosarcoma cells, gastric carcinoma cells, A549 non-small-cell lung cancer cells, chronic myeloid leukemia cells, MDA-MB-231 human metastatic breast cancer cells, and human colon cancer cells have been tested with carvacrol and has strongly supported the anticancerous potential of carvacrol [26, 33, 42, 43] (Figure 2). Al-Fatlawi et al., 2014 reported dose-dependent downregulation of the Bcl-2 gene and upregulation of the Bax gene in carvacrol-treated chemosensitive MCF-7 breast cancer cells. Carvacrol-treated MCF-7 cells also exhibited upregulated levels of caspase-3, 6, and 9 genes compared to untreated controls. This clearly illustrated the possible mechanism of apoptosis induction in carvacrol-treated cancer cells via p53 and mitochondrial pathway [44].

Arunasree et al. 2010 further investigated the molecular mechanism associated with the antitumor potential of carvacrol against MDA-MB-231 (metastatic) breast cancer cells. Clearly, it demonstrated that carvacrol treatment-induced dose-dependent apoptosis in MDA-MB-231 cells and decrease in MMP (mitochondrial membrane potential) of the cells, thereby leading to the cytochrome c release from mitochondria, caspase activation, and PARP (poly-ADP-ribose polymerase) cleavage [26]. FACS (flow cytometric) analysis of carvacrol-treated cells has further shown a significant increase of cells in the G0/G1 phase (apoptotic peak) and a decrease in the S phase, exhibiting apoptosis induction and DNA synthesis inhibition in the S phase [45].

The chemopreventive potential of carvacrol can also be attributed to the effect on hepatic steatosis, which may cause fibrosis, steatohepatitis, and cirrhosis recognized risk factor for HCC (hepatocellular carcinoma). Carvacrol has strong antioxidant properties parallel to butyl hydroxytoluene, ascorbic acid, and vitamin E [46]. Other reports have presented strong evidence about the anticancerous potential of carvacrol against Hep G2 HCC cells via inducing caspase-3 activation, PARP cleavage, and reduced Bcl-2 gene expression [47]. Additionally, carvacrol has been shown to cease cancer cell proliferation via reducing ERK1/2 phosphorylation and activating p38 phosphorylation in a dose-dependent manner [48, 49]. Similar effects have also been reported in DU145 (human prostate cancer) cells, where carvacrol treatment-induced ROS (reactive oxygen species) mediated apoptosis along with cell cycle arrest at G0/G1 in DU145 cancer cells [50].

Interestingly, carvacrol displayed stronger anticancerous potential against HCC cells and lung carcinoma cells, with limited cytotoxicity to normal human fetal liver cells. Recently, the interest in utilizing apoptosis induction as an effective strategy for elucidating potent antitumor drugs has escalated [51].

<p>| Table 1. In vitro antitumor activities of carvacrol and its possible targets. |
|------------------|-------------------|-------------------|------------------|-------------------|-------------------|
| <strong>Cancer</strong>     | <strong>Cell lines</strong>    | <strong>Doses (Range)</strong> | <strong>Anticancer mechanism</strong> | <strong>Molecular targets</strong> | <strong>References</strong> |
| Breast Cancer  | MDA-MB-231 cells | 1-10,000 µM       | Cell growth, inhibition; apoptosis induction, cell cycle arrest | Cyt c, Bax, cyclin A, B, CDK4 | [26, 52-54] |
|                 | MCF-7 cells       | 25-500 µM         | Cell cytotoxicity, cell growth inhibition, apoptotic induction, cell cycle arrest | p53, Bax, caspase 3/6/7, cyclin A, B CDK4 and 6, Cyclin D1, Bax, Bcl-2 PI3K/p-AKT | [44, 53-57] |</p>
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cell lines</th>
<th>Doses (Range)</th>
<th>Anticancer mechanism</th>
<th>Molecular targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cancer</td>
<td>Tca-8113</td>
<td>10–80 μM</td>
<td>Apoptosis induction</td>
<td>CCND1, CDK4, p21</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>N2a cells</td>
<td>10–400 mg/L</td>
<td>Anticancer and antioxidant potential</td>
<td></td>
<td>[77]</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>SH-SY5Y cells</td>
<td>12.5–50 μM</td>
<td>Cell growth inhibition</td>
<td>MYCN, Bax, Bcl2, TNFα</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td>N2a cells</td>
<td>10–400 mg/L</td>
<td>Anticancer and antioxidant potential</td>
<td></td>
<td>[77]</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Hep G2 cells</td>
<td>100-1000 μM</td>
<td>Cell growth inhibition, DNA damage, membrane damage, apoptosis induction</td>
<td>MAPK p-ERK 1/2 Caspase-3 Bcl-2, p-p38</td>
<td>[25, 36, 47, 48, 63, 65, 66]</td>
</tr>
<tr>
<td></td>
<td>Hep3B cells</td>
<td>1-1000 μM</td>
<td>Antiproliferative and cytotoxic effects</td>
<td></td>
<td>[63]</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>U87 cells</td>
<td>1–10,000 μM</td>
<td>Anticancer and antioxidant activity, apoptosis induction</td>
<td>PI3K/Akt, MAPK, TRPM7, MMP-2, p-Akt</td>
<td>[52, 74]</td>
</tr>
<tr>
<td></td>
<td>DBTRG-05MG cells</td>
<td>200–1,000 μM</td>
<td>Reduction in cell viability</td>
<td>Caspase-3 and ROS generation</td>
<td>[75]</td>
</tr>
<tr>
<td>Gastric adenocarcinoma</td>
<td>AGS cells</td>
<td>100–600 μM</td>
<td>Cell cytotoxicity, apoptosis induction</td>
<td>Bax, Bcl-2, GSH level, Caspase-3 and -9</td>
<td>[43, 73]</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>DU145 cells</td>
<td>10–500 μM</td>
<td>Cell growth inhibition via ROS mediated apoptotic induction</td>
<td></td>
<td>[50, 56, 67]</td>
</tr>
<tr>
<td></td>
<td>PC-3 cells</td>
<td>25–800 μM</td>
<td>Cell growth inhibition, cell migration and invasion apoptosis induction, caspase-8/9 activation</td>
<td>Bax, Bcl-2, Notch-1, Jagged-1, MMP-2, p-Akt, PI3K/Akt, TRPM7, IL-6, p-STAT3 p-ERK 1/2</td>
<td>[56, 67-71]</td>
</tr>
<tr>
<td>Melanoma</td>
<td>A375 cells</td>
<td>3.906–1,000 μg/mL</td>
<td>Reduction in cell viability, apoptotic induction</td>
<td>Bcl-2, cell cycle arrest</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>B16-F10 cells</td>
<td>-</td>
<td>Cell cytotoxicity</td>
<td></td>
<td>[72]</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>HeLa cells</td>
<td>25–800 μM</td>
<td>Cell growth inhibition via apoptotic induction</td>
<td>cyclin D1, BRK1/2, p21, caspase-3, ROS generation</td>
<td>[58-60]</td>
</tr>
<tr>
<td></td>
<td>SiHa cells</td>
<td>25–500 μM</td>
<td>Cell growth inhibition via apoptotic induction</td>
<td>Bax, Bcl-2, p53, caspase-3/6/9</td>
<td>[58, 61]</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>JAR cells</td>
<td>50–300 μM</td>
<td>Decreased cell viability, apoptosis induction</td>
<td>PI3K/AKT, p-JNK, p-ERK1/2 p-p38, MMP, ROS</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>JEG3 cells</td>
<td>50–300 μM</td>
<td>Decreased cell viability, apoptosis induction</td>
<td>PI3K/AKT, p-JNK, p-ERK1/2 p-p38, MMP, ROS</td>
<td>[62]</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>A549 cells</td>
<td>100–1,000 μM</td>
<td>Reduced Cell growth, apoptosis induction, cell migration inhibition</td>
<td>p38, NF-κB, TNF-α, GSK-3β, Beclin-1, AXL</td>
<td>[33, 35, 63, 64]</td>
</tr>
<tr>
<td></td>
<td>H460 cells</td>
<td>30–300 μM</td>
<td>Reduction in cell proliferation</td>
<td>AXL</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>H1299 cells</td>
<td>25–1800 μM</td>
<td>Decreased cell viability</td>
<td>Cell membrane and DNA damage</td>
<td>[34]</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>HT-29 cells</td>
<td>25–200 μM</td>
<td>Cell growth inhibition via apoptotic induction</td>
<td>CDK4 and 6 Cyclin D1, Bax, Bcl-2 PI3K/p-AKT</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td>Caco-2 cells</td>
<td>100–2,500 μM</td>
<td>Apoptosis induction, Cellular cytotoxicity</td>
<td>DNA damage</td>
<td>[38, 65, 66]</td>
</tr>
<tr>
<td></td>
<td>LoVo cells</td>
<td>100–900 μmol/L</td>
<td>Cell growth inhibition via apoptotic induction and cell cycle arrest</td>
<td>Bax-2, Bax MMP-2 and -9, Cyclin B1, p-ERK, p-JNK p-Akt PI3K/Akt</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td>HCT 116 cells</td>
<td>100–900 μmol/L</td>
<td>Cell growth inhibition via apoptotic induction</td>
<td></td>
<td>[39, 40]</td>
</tr>
</tbody>
</table>
Cancer | Cell lines | Doses (Range) | Anticancer mechanism | Molecular targets | References |
--- | --- | --- | --- | --- | --- |
Cancer | SCC-25 | 167 µg/mL | Apoptosis induction | Bcl-2 | [78] |
Ovarian cancer | OC2 cells | 200–1,000 µM | Decreased cell viability | Caspase-3, ROS generation | [79] |
Leukemia | SKOV-3 | 100-600 µM | Apoptosis induction | | [80] |
Leukemia | HL-60 cells | 10–400 µM | Cell growth inhibition | MMP, Bcl-2 | [81, 82] |
Leukemia | K562 cells | 200-1000 µM | Cell cytotoxicity | | [82, 83] |
Leukemia | KG1 cells | 100-400 µM | Reduction in Cell viability | | [82] |
Leukemia | CEM cells | 0.05–1.25 µM | Cell cytotoxicity | Cell cycle interruption | [55] |
Leukemia | P-815 | 0.05–1.25 µM | Cell cytotoxicity | Cell cycle interruption | [55, 84] |
Leukemia stem cells (CD123+/CD34+/CD38+) | 160 µg/mL | Cell growth inhibition via apoptotic induction | GSK-3β | [84] |

Abbreviations: Atg5/12, autophagy-related 5/12; Bax, Bcl-2 associated X protein; Bcl-2, B cell lymphoma 2; GSK-3β, glycogen synthase kinase 3 beta; LC3-II, light chain 3; PARP, poly (ADP ribose) polymerase; IKK, IκB kinase; MAPK, mitogen-activated protein kinase; MMP, mitochondrial membrane potential; N-myc proto-oncogene protein; NF-κB, nuclear factor-kappa; B ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

3. **In vivo efficacy of carvacrol**

Carvacrol administration has displayed significant anticancerous potential in Wistar rats via reduced tumor incidence and enhanced survival rate [42]. Carvacrol-treated animal models with DEN (diethylnitrosamine) induced liver cancer displayed reduced nodules and liver weight and increased body weight. Cells pretreated with carvacrol displayed the disappearance of most tumoral nodules and foci, characterized by some neoplastic cells, thereby validating the chemopreventive efficacy of carvacrol. Whereas carvacrol post-treatment demonstrated distorted cellular architecture, small persistent nodules, and a limited tendency to spread via intrahepatic veins. Moreover, carvacrol treatment resulted in increased levels of SOD (superoxide dismutase), CAT (catalase), GPx (glutathione peroxidase), GR (glutathione reductase), and GSH (glutathione), along with reduced lipid peroxides and several enzymes such as AST, LDH, ALT, γGT, and ALP in serum [85]. Subramaniyan et al. (2014) have further evaluated carvacrol's pre and post-treatment efficacy in a DEN-induced hepatocarcinogenesis rat model and reported stable tumor marker levels, reduced mast cell density, and cell proliferation. Moreover, carvacrol supplementation potentially restored the abnormal activities of liver microsomal xenobiotic-metabolizing enzymes with reduced PCNA (proliferative nuclear cell antigen), MMP-2, and -9 expression validating the antimetastatic efficacy of carvacrol [86]. Hence, carvacrol treatment in DEN (diethylnitrosamine) induced hepatocellular carcinoma rat model resulted in apoptosis induction characterized by DNA fragmentation. Additionally, carvacrol treatment showed a significant reduction in serum levels of AFP (alpha-fetoprotein), AFU (alpha L-fucosidase), VEGF (vascular endothelial growth factor), and reduced GGT (gamma-glutamyl transferase) gene expression [60]. Carvacrol supplementation further displayed significant improvement in the growth rate of DMH (1,2-dimethylhydrazine) induced animal model of colon cancer with lower incidence of pre-neoplastic lesions and tumors, along with reduced oxidative stress damage (increased levels of SOD, GSH, CAT, GPx, and GR) thereby strongly validating the chemopreventive potential of carvacrol [87]. Li et al. (2019) further showed limited tumor growth in the carvacrol-treated
DEN-induced hepatocarcinoma mice model, thereby displaying tumor cell reduction, normal cell arrangements, rare mitotic figures microvessels, and reduced peritumor and intrastromal lymphocytes. Similarly, there was reduced DAPK1 (death-associated protein kinase 1) and PPP2R2A (serine/threonine-protein phosphatase 2A) expression in tumor tissues [88]. Another recent study has presented better anticancerous efficacy of carvacrol in DMBA (dimethylbenzanthracene) induced breast cancer in female Holtzman rats by displaying a 75% reduction in tumor frequency, 67% reduction in tumor incidence, and a significant reduction in tumor volume [89]. Additionally, carvacrol has exhibited significant anticancerous potential via regulating numerous cell signaling and apoptotic pathways.

**Table 2. In vivo antitumor activities of carvacrol and its possible targets.**

<table>
<thead>
<tr>
<th>Cancer Model</th>
<th>Cell lines</th>
<th>Doses/treatment</th>
<th>Anticancer mechanism</th>
<th>Molecular targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>DMBA-induced induced breast cancer in the female Holtzman mice</td>
<td>50, 100, and 200 mg/kg carvacrol for 14 weeks orally</td>
<td>Reduction in number of tumors</td>
<td>Antioxidant activity</td>
<td>[89]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>DMH-induced induced colon cancer in male Wistar rats</td>
<td>20, 40, and 80 mg/kg carvacrol daily for 16 weeks i.p.</td>
<td>Tumor growth inhibition</td>
<td>Increased level of GPx, GR, GSH, SOD, CAT</td>
<td>[87]</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>0.01% DEN induced hepatocellular carcinoma in Wistar rats</td>
<td>15 mg/kg carvacrol for 16 weeks orally</td>
<td>Chemopreventive effects and apoptosis induction</td>
<td>Increased serum marker enzymes AST, ALT, ALP, LDH, cGT</td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td>N-nitrosodimethylamine induced hepatocellular carcinoma in Wistar rats</td>
<td>15 mg/kg carvacrol for 15 weeks orally</td>
<td>Antiproliferative antiangiogenic and apoptosis-inducing effects</td>
<td>Decrease AFP, VEGF, AFU, and GGT PARP, DNA ligase, and polymerase beta</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>0.01% DEN induced hepatocellular carcinoma in Wistar rats</td>
<td>15 mg/kg carvacrol for 16 weeks orally</td>
<td>Decrease tumor growth</td>
<td>Decrease tumor markers, MMP-2 and - 9, AgNORs, PCNA</td>
<td>[86]</td>
</tr>
<tr>
<td></td>
<td>DEN-induced hepatocellular carcinoma in C57BL/6 mice</td>
<td>Intragastrically for 20 weeks</td>
<td>Decrease tumor growth</td>
<td>Modulation of DAPK1 and PPP2R2A</td>
<td>[88]</td>
</tr>
</tbody>
</table>

Abbreviations: HPV, human papillomavirus; COX-2, cyclooxygenase-2; I.P., Intraperitoneal; INK, c-Jun N-terminal kinase; PARP, poly-ADP ribose polymerase; VEGF, vascular endothelial growth factor; ROS, reactive oxygen species;

**4. Conclusions**

Amongst numerous phyto-compounds, carvacrol contributes to potent anticancerous effects. Carvacrol has been presented to utilize several mechanisms for obstructing carcinogenesis via modulating various deregulated cell signaling pathways associated with apoptosis, autophagy, inflammation, and angiogenesis. Carvacrol has been shown to interfere with several intracellular signaling molecules, including ILs, TNF-α, Bax, VEGF, Beclin, caspasases, and Bcl-2. This review has presented several in vitro and in vivo research studies to validate the strong anticancerous potential of carvacrol via targeting several potential therapeutic targets, including Bcl-2, Bax, NF-κB, p53, caspasases, Akt, TNF-α, and GSH. Despite various preclinical mechanistic research reports on the anticancerous potential of carvacrol, the lack of well-designed clinical trials exhibiting the therapeutic efficacies of carvacrol enhanced the urge for elucidating better significant clinical studies. Still, more extensive and elaborative studies are needed to develop a more potent targeted drug delivery system for cancer management. Studies should be aligned towards exploring the novel molecular targets of carvacrol and its associated mechanism in different cancers. Altogether, carvacrol has vast medicinal health potential and, therefore, should be utilized as a potential therapeutic agent via extensive investigation of its anticancerous potential.
Funding

This research received no external funding.

Acknowledgments

The authors thank Noida Institute of Engineering and Technology management for providing the facilities to carry out this study.

Conflicts of Interest

The authors declare no conflict of interest.

References


https://biointerfaceresearch.com/


