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Synergistic Anticancer And Antioxidant Effects Of Eugenol And Baicalin

Vikas Sharma[1,2], Arti Gupta[3,4], Shaivi Parashar[2], Rahul Kaushik[2], Sandeep Kumar[1,5*]

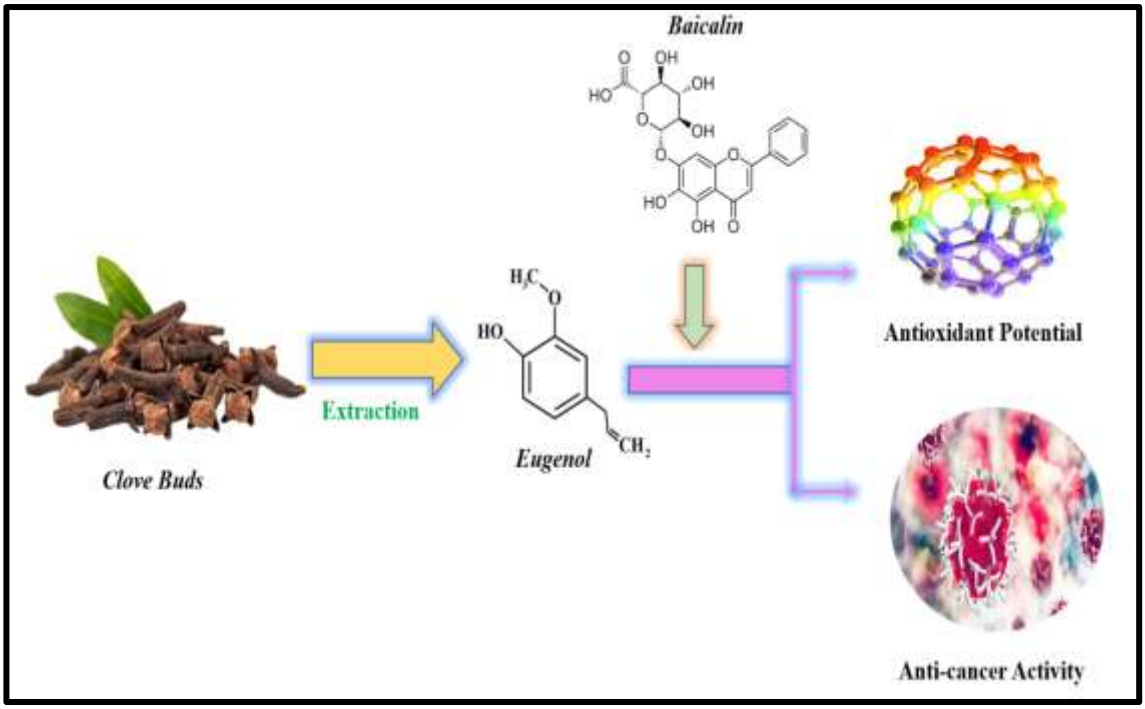
[1] School of Pharmacy, Sharda University, Greater Noida, India
[2] Metro College of Health Sciences and Research, , Greater Noida, India
[3] Lloyd Institute of Management and Technology, Greater Noida, Uttar Pradesh, India
[4]Lloyd School of Pharmacy, Greater Noida, Uttar Pradesh, India
[5*]DST-FIST Lab, Sharda University, Greater Noida, Uttar Pradesh, India
*Corresponding Author; Sandeep Kumar
*E. Mail id: ph.sandeep@gmail.com

ABSTRACT

This study investigates the anticancer and antioxidant potential of a novel phytochemical combination of eugenol, a natural compound extracted from cloves, and baicalin, a flavonoid from Scutellaria baicalensis. The synergistic interaction between eugenol and baicalin was found to exhibit moderate cytotoxicity against MCF-7 cell lines, with an IC50 value of 147.2 μM, suggesting potential anti-cancer properties. The combination also demonstrated potent antioxidant activity, comparable to quercetin, in DPPH and H2O2 scavenging assays. The results suggest that the eugenol-baicalin combination may have therapeutic applications in the prevention and treatment of oxidative stress-related diseases and cancer. Further studies are needed to fully elucidate the mechanisms of action and optimal dosing regimens. Overall, this study highlights the potential of combining natural compounds to create novel antioxidant and anti-cancer agents, and underscores the importance of continued research into the therapeutic properties of plant-derived compounds.

Keywords: *eugenol, baicalin, antioxidant, cytotoxicity, synergism*

Graphical Abstract



1. INTRODUCTION

For centuries, cloves have been a prized medicinal spice, with their primary active compound, eugenol, being utilized for its diverse therapeutic properties(Pferschy-Wenzig et al., 2015; Safarzadeh et al., 2014a). Eugenol has

been employed as a topical anesthetic, dental adjunct, and has recently garnered attention for its potential in treating various ailments. The essential oil of cloves, extracted through steam distillation of the dried flower buds of Syzygium aromaticum L., an evergreen tree, serves as the primary source of eugenol(Chatzinasiou et al., 2019; Safarzadeh et al., 2014b). Further analysis of the essential oil reveals a secondary constituent, acetyl eugenol (eugenol acetate), which shares a similar chemical structure and exhibits promising medicinal benefits. Additionally, the essential oil contains a array of minor components, including terpenes, which are commonly found in plant-derived essential oils and contribute to their therapeutic profiles. Eugenol has been shown to possess anti-inflammatory, antimicrobial, and antioxidant properties, making it a valuable compound in traditional medicine(Amtaghri et al., n.d.). Acetyl eugenol has been found to exhibit analgesic, anti-inflammatory, and antimicrobial activities, warranting further research into its potential medicinal applications. The terpenes present in clove essential oil, such as beta-caryophyllene and alpha-humulene, have been reported to possess anti-inflammatory and antimicrobial properties, contributing to the oil's therapeutic effects(Desai et al., 2008; Morigi et al., 2012). The synergistic interactions between eugenol, acetyl eugenol, and terpenes may enhance the medicinal benefits of clove essential oil, making it a valuable adjunct therapy in various healthcare applications(Amtaghri et al., n.d.).

Eugenol and Baicalin have shown remarkable anticancer potential through various mechanisms. Clove's primary constituent, Eugenol, exhibits antiproliferative effects, inhibiting cancer cell growth and inducing apoptosis, while also showcasing antioxidant and anti-inflammatory properties(Pferschy-Wenzig et al., 2015; Xiong et al., 2022). Clove extract has been shown to inhibit tumor growth and angiogenesis, inducing apoptosis in various cancer cell lines. Baicalin, a flavonoid from Scutellaria baicalensis, also exhibits antiproliferative effects, anti-inflammatory properties, and antioxidant activity, inhibiting tumor growth and metastasis, and inducing apoptosis in various cancer cell lines(Clark, 1991; Crossman et al., 2018; Shuvalov et al., 2023). Both clove and baicalin (figure 1) share common mechanisms, inhibiting NF-κB and modulating the PI3K/Akt signaling pathway, which regulates cell survival and proliferation. Additionally, they exhibit antimicrobial properties, potentially preventing cancer-promoting infections(Ardies, 2003; Hanahan et al., 2011; Sung et al., 2021). While these findings are promising, further research is needed to fully understand their anticancer potential and explore possible applications in cancer prevention and treatment(Umezawa et al., 2019; Wong et al., 2019). In this research, we have evaluated anticancer potential of eugenol in combination with baicalin.

Figure 1 Scutellaria baicalensis (Baicalin) [A]. Syzygium aromaticum (Clove) [B].

2. MATERIAL AND METHODS

Clove buds, obtained in their dried form from a local supermarket, were processed into a fine powder using a coffee bean grinder. This step ensured a uniform particle size of 20-mesh, thereby maximizing the surface area and enhancing the efficiency of subsequent extractions. The powdered cloves were then prepared for extraction and analysis. The necessary solvents, including isopropanol, ethyl acetate, hexane, and chloroform, were sourced from GLR Innovations, a reputable supplier of laboratory chemicals. Additionally, MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) dye and DMSO (Dimethyl sulfoxide) were also acquired from GLR Innovations for use in the bioactivity assays. Baicalin, a flavonoid compound, was generously provided as a gifted sample by Edudap Chemicals Suppliers. This enabled the investigation of its potential bioactive properties in conjunction with the clove extracts. By acquiring these materials, the stage was set for a comprehensive analysis of the bioactive properties of cloves and baicalin, including their potential anticancer and antimicrobial activities.

2.1 Extraction

Extracting eugenol from cloves involves a multi-step process beginning with grinding the cloves into a fine powder to increase the surface area and facilitate efficient extraction(Agarwal Scholar et al., 2017; Simándi et al., 1999). Next, the powdered cloves are mixed with water and subjected to distillation, where the mixture is heated, causing the water and eugenol to vaporize, and then condensed and collected in a separate container, repeating the process until approximately 25 mL of distillate is obtained(Hudz et al., n.d.; Ibrahim et al., 2015). The distillate is then transferred to a separation funnel, where it is mixed with diethyl ether, allowing the ether to extract the eugenol from the water, resulting in two distinct layers, with the top layer containing the eugenol and diethyl ether being separated from the bottom layer(Oliveira et al., 2021).

The top layer is then transferred to an Erlenmeyer flask, where small portions of magnesium sulfate are added to absorb any remaining water, followed by filtration to remove the magnesium sulfate, yielding a dry and clear solution(Pardo-Mates et al., 2017; Russell et al., 1999). Finally, the filtered liquid is placed in a beaker and subjected to a steam bath, where the heat causes the diethyl ether to evaporate, leaving behind a concentrated solution of eugenol, with the steam bath continued until only 1-2 mL of solution remains, resulting in a highly concentrated eugenol extract, which can then be further purified and analyzed for its chemical composition and potential applications(Pinho et al., 2023; Su et al., 2021). Throughout this process, careful attention is paid to temperature, solvent ratios, and extraction times to optimize the yield and characterized using IR spectroscopy as depicted in figure 3 and table 1.

2.2 Free radical scavenging Activity

The DPPH (2,2-diphenyl-1-picrylhydrazyl) solution was prepared by dissolving 2.4 milligrams of DPPH in 100 milliliters of methanol, creating a solution containing oxidative moieties(Imran et al., 2020; Qi et al., 2022). This solution serves as a reference for measuring the antioxidant activity of the sample extract. To assess the antioxidant potential, 4 milliliters of the DPPH solution was combined with 5 microliters of the sample extract in a cuvette. The mixture was vigorously agitated for 10 minutes to ensure thorough mixing, followed by incubation in the dark for 30 minutes to allow the reaction to reach completion. After incubation, the absorption of the resulting solution was measured using UV spectrophotometry at a wavelength of 550 nanometers(Aydin et al., 2013). This measurement quantifies the degree of DPPH reduction, which is directly related to the antioxidant activity of the sample extract. By comparing the absorption values, researchers can determine the extract's ability to neutralize oxidative moieties, providing valuable insights into its potential antioxidant properties.

To prepare a 40 mM hydrogen peroxide solution, a precise mixture of hydrogen peroxide and phosphate buffer solution was required. Specifically, 4.09 milliliters of hydrogen peroxide was added to 1000 milliliters of phosphate buffer solution, which had been previously adjusted to a pH of 7.4(Kima et al., 2016). This ensured that the resulting solution had the desired concentration and pH for the subsequent assay. Next, 0.24 milliliters of the drug extract solution was added to 2.4 milliliters of the freshly prepared 40 mM hydrogen peroxide solution. The mixture was then vigorously shaken to ensure thorough mixing of the two solutions. Following mixing, the solution was placed in a dark environment for 20 minutes to allow the reaction to proceed without any external influences(Jiang et al., 2019; Shuvalov et al., 2023). This incubation period allowed the antioxidant properties of the drug extract to manifest and interact with the hydrogen peroxide. Finally, the absorbance of

both the mixture and a control solution (hydrogen peroxide solution without drug extract) was measured at a wavelength of 560 nanometers using UV spectrophotometry(Choudhury Barua et al., 2014; Marques et al., n.d.).

2.3 Cell Line Maintenance

MCF-7 cell line was Procured from NCCS Pune. The cells were harvested from flask at 90% confluency and seeded in 96 well plates at appropriate density in DMEM medium (Dulbecco's Modified Eagle Medium-AT149-1L) supplemented with 10% FBS (Fetal Bovine Serum - HIMEDIA-RM 10432) and 1% antibiotic solution at 37°C with 5% CO_2(Fu et al., 2012; Shao et al., 2020). Next day, medium was removed and fresh culture medium was added to each well of the plate. 10% of the total medium (5 to 50µl) of Treatment dilutions (of different concentrations) were added to the defined wells and treated plates were incubated (Heal Force-Smart cell CO_2 Incubator-Hf-90) for 24 h(Bars-Cortina et al., 2022; Eiermann et al., 2001).

2.4 Cytotoxicity Assay

Cytotoxicity of the provided samples on MCF-7 (Procured from NCCS Pune) cell line was determined by MTT Assay(Nguyen Thi Thu et al., 2023; Thu et al., n.d.). The cells (10000 cells/well) were cultured in 96 well plate for 24 h in DMEM medium supplemented with 10% FBS and 1% antibiotic solution at 37°C with 5% CO_2. Next day cells were treated from (as per mention in the excel sheet) of the formulations (different concentrations were prepared in incomplete medium)(Ghelichkhani et al., n.d.). After incubation for 24 hours, MTT Solution (a final concentration of 250µg/ml) was added to cell culture and further incubated for 2 h. At the end of the experiment, culture supernatant was removed and cell layer matrix was dissolved in 100 µl Dimethyl Sulfoxide (DMSO) and read in an Elisa plate reader (iMark, Biorad, USA) at 540 nm and 660 nm. IC_{50} was calculated by using software Graph Pad Prism -6. Images were captured under inverted microscope (Olympus ek2) using Camera (AmScope digital camera 10 MP Aptima CMOS)(Agrawal et al., 2011; Elkashty, 2020).

3. RESULTS AND DISCUSSION

3.1Free radical scavenging activity

DPPH % scavenging activity of the novel phytochemical combination was performed against quercetin (As a standard). The DPPH radical scavenging potentiality of combination and quercetin were approximately equal in 200 µg/mL concentration. But 600 µg/mL solution of quercetin shows the 57% inhibition against DPPH while combination have shown 51% inhibition against DPPH as given in figure 2.

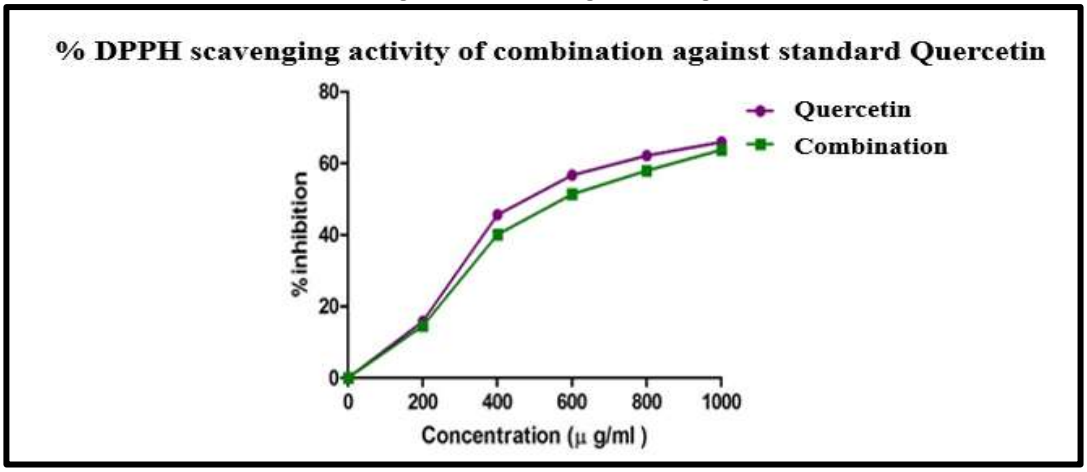


Figure 2 DPPH % Scavenging Activity of Novel Phytochemical Combination

The results for the percentage H_2O_2 scavenging activity have been discussed as the percentage H_2O_2 scavenging activity in Figure no. . Quercetin was used as the standard. In the starting there was a difference in the % inhibition of Hydrogen peroxide at 200 µg/mL while at 600 µg/mL solution of combination have shown the same % inhibition as the standard quercetin shows as depicted in figure 3.

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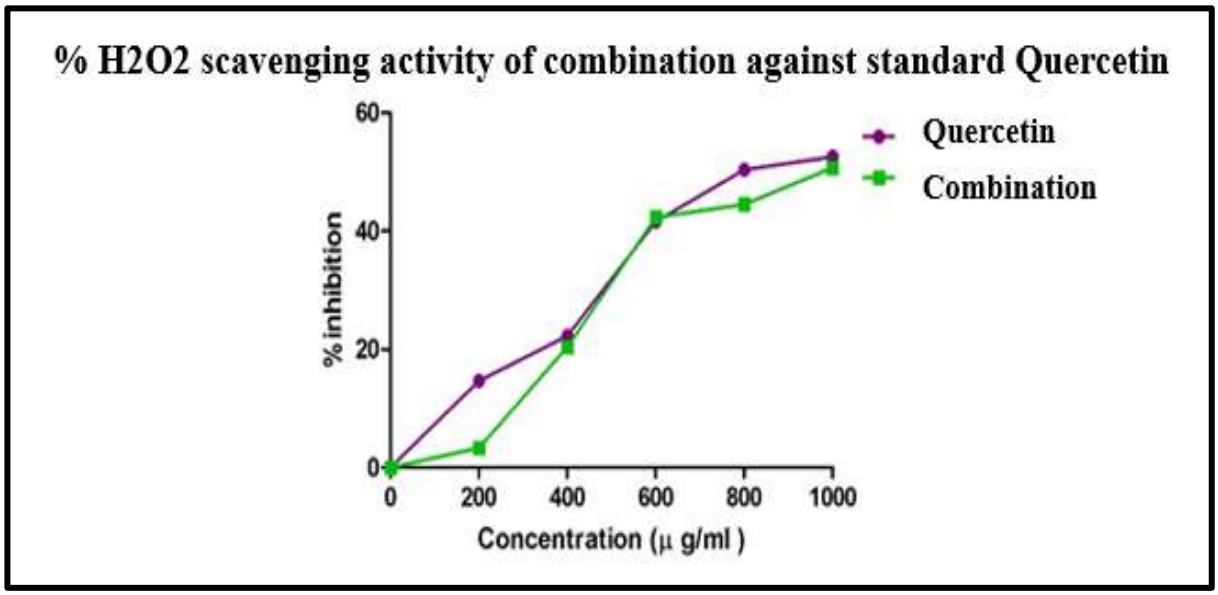

Figure 3 H2O2 % Scavenging Activity of Novel Phytochemical Combination

3.2 Infra-red Spectroscopy of Eugenol

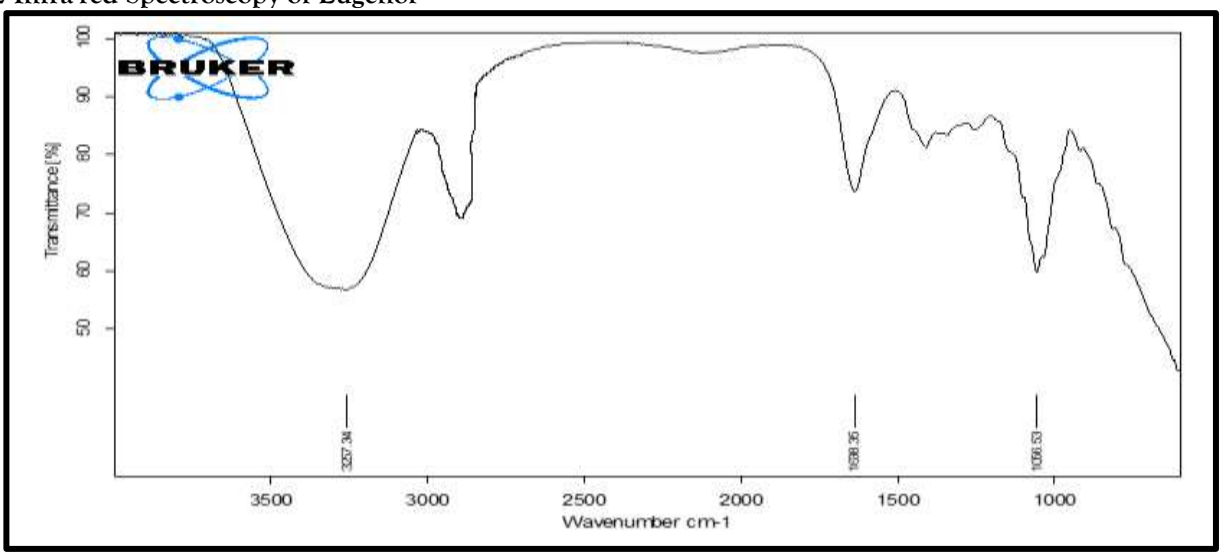

Figure 4 Infra-Red Spectroscopy of Eugenol extracted from clove buds

Table 1 depicts IR interpretation of eugenol.

Wavenumber	Nature of Peak	Proposed Structure
3257-3400 cm^{-1}	Broad medium	Alcoholic and methoxy group
2835 cm^{-1}	Single peak with W shape	Methyl group
1638 cm^{-1}	Single, small intense	C=C stretching (Aromatics)
1056 cm^{-1}	Medium Intense	C-O stretching

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3.3 Cell Culture Maintenance

MCF-7 cells were grown in DMEM medium; images shown in following figure 5.

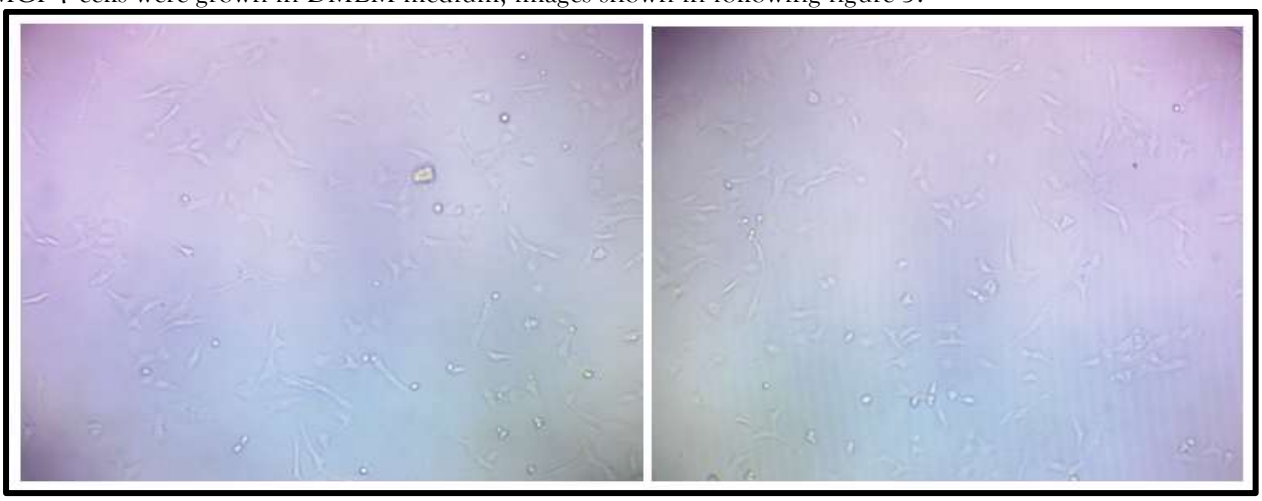

Figure 5 MCF-7 Cell lines growing in DMEM medium with the aid of FBS and PenStrep Solution

3.4 Cytotoxicity Assay

Based on the results obtained from the MTT assay, it was observed that when the MCF-7 cell line was exposed to different concentrations of the sample, moderate cytotoxic activity was observed with the administration of novel phytochemical combination (IC_{50} = 147.2 ± 0.098 µM) as given in figure 5. The IC_{50} is the concentration of an inhibitor/sample/ formulation at which the viable cells reduced by half.

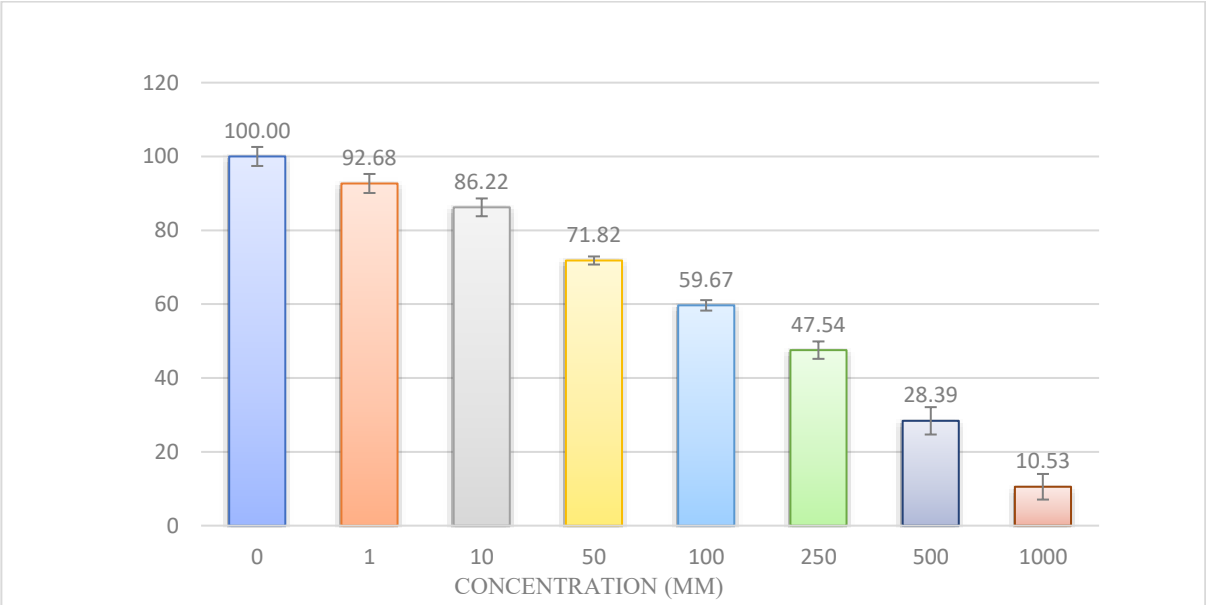

Figure 6 MTT Data analysis of novel phytochemical combination.

The present study successfully extracted eugenol from cloves and evaluated its antioxidant potential in combination with baicalin. The IR spectroscopy analysis confirmed the presence of eugenol, which was then combined with baicalin to create a novel antioxidant mixture. The DPPH and H2O2 scavenging assays revealed that this combination exhibited potent antioxidant activity, comparable to the standard antioxidant quercetin, at a concentration of 600 µg/mL. This suggests that the synergistic interaction between eugenol and baicalin enhances their individual antioxidant properties.

The MTT assay revealed an IC50 value of 147.2 µM, indicating moderate cytotoxicity against MCF-7 cell lines. This suggests that the novel combination may have potential anti-cancer properties, although further studies are

needed to confirm this. The antioxidant and cytotoxicity results suggest that the eugenol-baicalin combination may have potential therapeutic applications, particularly in the prevention and treatment of oxidative stress-related diseases and cancer. However, further studies are needed to fully elucidate the mechanisms of action and optimal dosing regimens. Overall, this study demonstrates the potential of combining natural compounds to create novel antioxidant and anti-cancer agents, and highlights the importance of continued research into the therapeutic properties of plant-derived compounds.

4. CONCLUSIONS

The study underscores the remarkable anticancer and antioxidant potential of the synergistic combination of eugenol and baicalin, showcasing moderate cytotoxicity against MCF-7 cell lines and pronounced free radical scavenging activity. The observed bioactivity of this novel phytochemical combination is a testament to the potential benefits of integrating natural compounds in the development of innovative therapeutic strategies.
The moderate cytotoxicity exhibited by the eugenol-baicalin combination against MCF-7 cell lines suggests that this phytochemical duo may be a valuable adjunct in the treatment of certain types of cancer, particularly those characterized by oxidative stress and inflammation. Moreover, the significant free radical scavenging activity demonstrated by this combination highlights its potential in mitigating oxidative stress-related diseases, such as neurodegenerative disorders and cardiovascular disease. The findings of this study suggest further investigation to fully elucidate the mechanisms of action underlying the anticancer and antioxidant effects of the eugenol-baicalin combination. Additionally, further research is needed to optimize the dosing regimens, evaluate the efficacy of this combination in vivo, and explore its potential applications in the prevention and treatment of various diseases. Nevertheless, the present study provides a promising foundation for the development of novel phytochemical-based therapeutic approaches, underscoring the importance of continued research into the medicinal properties of plant-derived compounds.

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AUTHOR CONTRIBUTIONS

V. Sharma: Original Draft and work completion, **A. Gupta-** Revision of data analysis and manuscript **S. Parashar:** Images preparation, **R. Kaushik:** Data analysis and corrections. **S. Kumar:** Supervision, Data Analysis and Formatting,

DECLARATION

We declare that all authors of this manuscript have done substantial contribution. We didn't exclude any author who substantially contributed to this manuscript. We have also followed all the ethical norms established by our respective institutions.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

ETHICAL APPROVAL

Not Applicable.

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