Ethnomedicinal uses and phyto-pharmacological activities of Cumin: A literature-based review

A dissertation submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University in the partial fulfilment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

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May, 2023

APPROVAL

The title of this project paper is "**Ethnomedicinal uses and phyto-pharmacological activities of Cumin: A literature-based review**" submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been approved as its style and content and has been acknowledged as satisfactory for the partial fulfillment of the criteria for the degree of Bachelor of Pharmacy.

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CERTIFICATE

This is to certify that the results of the investigation that are embodied in this project entitled **"Ethnomedicinal uses and phyto-pharmacological activities of Cumin: A literature-based review"** are original and have not been submitted before in substance for any degree of this University. The entire present work submitted as a project work for the partial fulfillment of the degree of Bachelor of Pharmacy, is based on the result of author's (Mohsina Rahman Bonna, Id: 191-29-221) own investigation.

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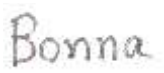
DECLARATION

I hereby declare that I carried out this project under the supervision of Md. Mizanur Rahman, Assistant Professor, Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, for partial fulfilment of the requirement for the degree of Bachelor of Pharmacy (B. Pharm.). This project, I declare, is my original work. I also state that neither this project nor any part thereof has been submitted for award or any degree elsewhere.

Submitted by



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ACKNOWLEDGEMENT

First and foremost, I convey my whole hearted gratitude to Almighty Allah for giving me strength, courage and endurance to complete the project work.

I wish to express my sincere thanks to Professor Dr. Muniruddin Ahmed, Head, Department of Pharmacy, Daffodil International University for providing me with all the necessary facilities for the project.

I would like to express my best regards, heartfelt gratefulness, deep appreciation to my honorable, amicable, dynamic and beloved supervisor, Md. Mizanur Rahman, Assistant Professor, Department of Pharmacy, Daffodil International University for providing me continuous support and guideline to perform this project work and to prepare this concerted dissertation. His support to me can only be acknowledged but never be compensated. His consistent inspiration helped me to work diligently throughout the completion of this project work and also contributed to my ability to approach and solve a problem. Without his continuous guidance this dissertation would not has been materialized.

I would like to offer my extraordinary indebtedness and gratitude to my respectable teachers of the Department of Pharmacy for their valuable suggestions, inspiration and support during the course of my project work.

I would like to extend my thanks to all my juniors, senior brothers for their help during the project work. I am also thankful to my well-wishers for their help and encouragements during the completion for this project work.

I would like to express my indebtedness gratitude to my parents and family members who inspired and supported me throughout my project work.

Finally, I offer my gratitude to one and all, who directly or indirectly, have put their hand in this venture.

Author

May, 2023

"Dedicated to my parents"

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ABSTRACT

Spices have been described as the fundamental blocks that provides aroma and taste to the foods. Cumin (*Cuminum cyminum* L.), commonly referred to as 'Jeera' or 'Zeera', is a popular culinary spice recognized for its aromatic impact belonging in the family Apiaceae. This review explores the taxonomic, nutritional, ethnomedical, phytochemical, and pharmacological uses of cumin. It displays a variety of gastronomic, ethnic, and curative properties. Traditional uses of the plant include diuretic, antispasmodic, antiepileptic, antispasmodic, and carminative properties. A number of phytochemicals, including as alkaloids, coumarin, anthraquinone, flavonoids, glycosides, proteins, resin, saponin, tannin, and steroids, are present in *Cuminum cyminum* which are responsible for a number of therapeutic promises. The primary bioactive, which accounts for the majority of its pharmacological relevance, is cuminaldehyde. Cumin possesses powerful antioxidant, anti-inflammatory, analgesic, antibacterial, antidiabetic, anticancer, hepatoprotective, gastrointestinal, and anti-osteoporotic properties.

Keywords: Cuminum cyminum L., Traditional uses, Phytochemicals, Cuminaldehyde, Pharmacological activities

LIST OF ILLUSTRATIONS

LIST OF ABBREVIATIONS

MPO	Myeloperoxidase
FRAP	Ferric reducing antioxidant power assay
DPPH	2,2- diphenyl-1-picrylhydrazyl
ABTS	2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid)
FIC	Ferrous iron chelating assay
SRB	Sulphorhodamine B
MTT	3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
PTZ	Pentylenetetrazole
GABA	γ-aminobutyric acid,
nAChR	Nicotinic acetylcholine receptor
$GABA_AR$	γ-aminobutyric acid A receptor
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum glutamic-oxaloacetic transaminase

CHAPTER ONE

INTRODUCTION

1. Introduction

Spices have been described as the fundamental blocks that provides aroma and taste to the foods. They are essential bio nutrients for both food and dietary supplements. Since the dawn of time, spices have been applied to boost the flavor and taste of food (Mughal, 2022). Additionally, they function as additives while offering dietary as well as medical benefits. Spices also have a wide range of therapeutic characteristics that are utilized in the Ayurvedic Pharmacopoeia to treat a wide range of illnesses. Due to their bactericidal, bacteriostatic, fungistatic, antifertility, anthelminthic, and other therapeutic characteristics, spices are becoming an increasingly important ingredient in Indian cuisine. Many spices and herbs are found to show a variety of therapeutic benefits, including antithrombotic, anti-atherosclerotic, hypolipidemic, anti-inflammatory, anti-aggregatory, and eicosanoid inhibitor properties (Singh et al., 2017).

1.1 Cumin

Cumin (Cuminum cyminum), commonly referred to as 'Jeera' or 'Zeera', is a popular culinary spice recognized for its aromatic impact. Because it was a symbol of fidelity and love during the Middle Ages, cumin is a traditional and widely used spice. The qualities of cumin, which comes in a variety of looks including anise, fennel, and black cumin, make them distinct from one another. The seeds of cumin contain fixed oil, volatile oils, acids, essential oils, protein, and other substances, according to a proximate study. Numerous disorders have been addressed employing cumin and its active ingredients, particularly pinene, cymene, terpinene, cuminaldehyde, oleoresin, and thymol. Cumin has demonstrated a number of advantages due to the availability of nutrients. For energy, immune systems, breastfeeding, and skin conditions, iron is a crucial component (Srivastava, 19889).

Figure 1: Cumin plant

Three colors of cumin seeds are available: amber (the most frequently distributed), white, and black (both found in Asian markets). Cumin seeds have a fragrant, nutty flavor. Amber and white cumin seeds can be used interchangeably, but the black seed has a richer, pepperier flavor. One of the primary components of curry powders is cumin, which gives most Indian cuisine its distinct aroma when combined with coriander leaves. India produces 70% of the world's supply and consumes 90% of it (which implies India consumes 63% of the world's cumin). Turkey (6%), Iran (6%), and Syria (7%), on the other hand, are manufacturers. Other countries account for the remaining 11% (Dar et al., 2019).

1.2 Harvesting

Cumin is of the oldest and most valuable plant species, its cultivation typically demands a three to four-month long, intense summer with typical daytime temperatures of at least 308 degrees (Hajlaoui, 2010). Cumin is manually collected from plants that reach a height of 30–50 cm (12–20 in). It is an annual herbaceous plant with a stem that is 20–30 cm (8–12 in) tall, 3-5 cm (1+14–2 in) in diameter, and is branching (Sastry, 2013).

1.3 Taxonomic Hierarchy

Kingdom	Plantae
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta
Superdivision	Embryophyta
Division	Tracheophyta
Subdivision	Spermatophyta
Class	Magnoliopsida
Superorder	Asteranae
Order	Apiales
Family	Apiaceae
Genus	*Cuminum L.*
Species	*Cuminum cyminum L.*

1.4 Geographical distribution

Although its precise origins are unknown, cumin is believed to have originated in the region that stretches from the southernmost Mediterranean to central Asia (previously known as Turkestan). The use of cumin dates back to ancient times. The countries with the highest levels of cultivation at the moment include China, India, Morocco, Cyprus, Egypt, Turkey, Iran, and southern Russia. (Jansen, 1981; Husain et al, 1988). Other parts of the world only occasionally practice cultivation; in South-East Asia, only mountainous regions (such as Indonesia) do so. The primary producer and consumer of C. cyminum is India. The two states that produce the most cumin in India are Rajasthan (56%) and Gujarat (44%) (Singh, 2021).

1.5 Nutritional value

Seeds of cumin account for a large portion of the Daily Value for fat (particularly monounsaturated fat), protein, and dietary fiber in a 100-g reference quantity (table). There are significant Daily Value quantities of B vitamins, vitamin E, and a number of dietary minerals, particularly iron, magnesium, and manganese (table). Petroselinic acid is found in cumin seeds (Bettaieb et al., 2011; Hewlings & Kalman, 2011).

1.6 Useful parts of cumin

1.6.1 Leaves

Cumin has multi-fid leaves with lengthy filiform segments.

1.6.2 Flowers

The bracts, which are produced after flowering, cover the tiny, white, or pink flowers. Both partial and general umbels have around five rays, and the involucres have two or three filiform, one-sided bracts.

1.6.3 Fruits

The ovate or fusiform, light brown or whitish fruits of cumin are. The fruit resembles caraway but is larger, about a couple of lines long, significantly longer than the pedicels, almost tapering, but slightly constrained at the sides, fusiform, and sealed by the short calyx teeth. It is densely covered in short, rough hair upon the channels and less densely upon the ridges, which are paler,

filiform, and slightly; The two seeds or half-fruits are oblong and plano convex, with the plane surfaces coming together (L.). The cumin fruit has a flavor and aroma almost same to caraway, despite being substantially warmer and less pleasant (De et al., 2003).

1.6.4 Seeds

The cumin seed has nine protuberances, is elongated, and varies in color from yellow to brownish gray. It has a wide range of therapeutic benefits. The properties of cumin seeds are cooling, astringent, stimulating, stomachic, carminative, fragrant, and synergistic. Cumin seed oil is employed in topical clothing ointments and multipurpose luminous paints. An astringent and aromatic herb, cumin is good for the digestive system (Chaudhry et al, 2012).

Figure 2: Different plant parts of Cumin

1.7 Objectives of the study

1.7.1 General objectives

The study is aimed to collect and summarize up-to-date data of a popular spice cumin from various database reports.

1.7.2 Specific objectives

1. To collect various data available on the phytochemical, medicinal and pharmacological activities of cumin based on various database reports.
2. To summarize all the updated data based on various activities.
3. To include the possible mechanism for the pharmacological activities of cumin.

CHAPTER TWO

METHODOLOGY

2. Methodology

This study was carried out to report and assimilate all previously published articles on phytochemical, medicinal and pharmacological activities of cumin. In order to find publications published until December 2022, the following databases were used: Google Scholar, PubMed, Springer Link, Elsevier, Science Direct, Scopus Web of Science, and Biomed Central. Total 1172 articles were found out of which 78 articles were considered relevant according to inclusion and exclusion criteria. The references listed in the chosen articles were also read, and if they satisfied the inclusion requirements of our search, they were included. The articles were integrated and tallied chronologically, starting with the most current and ending with the oldest, using information acquired from several databases. The redundant articles were subsequently eliminated using inclusion and exclusion criteria after each article had been carefully examined.

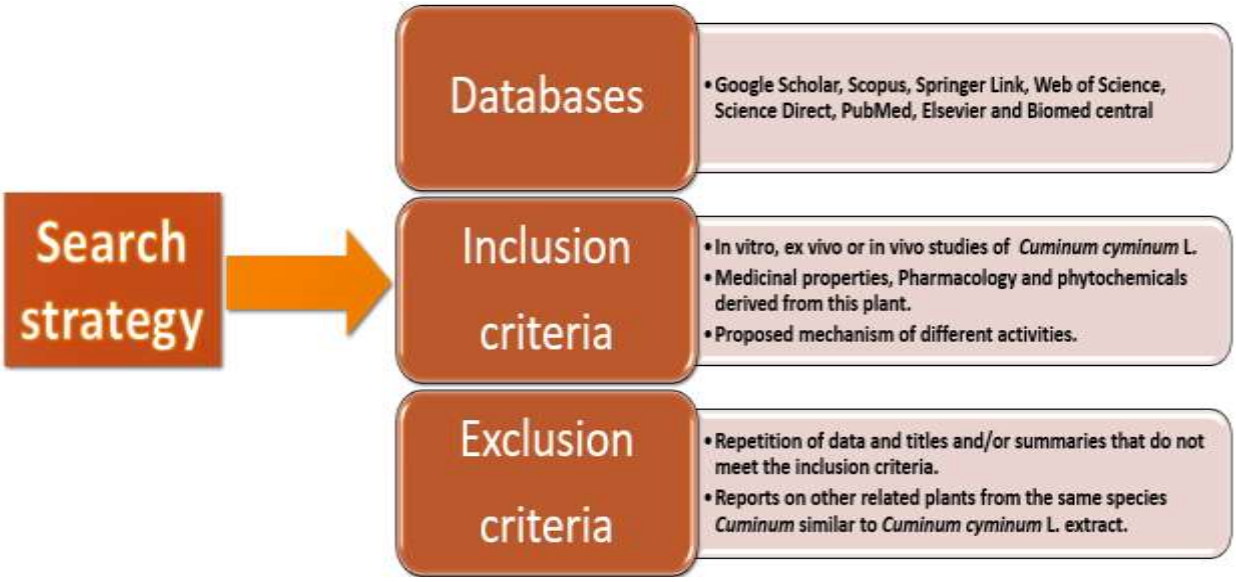

Figure 3: Schematic methodology

CHAPTER THREE

RESULTS AND DISCUSSION

3. Results and discussion

3.1 Ethnomedicinal uses

One of the most widely used seed types, cumin has a long history of use in the food, beverage, alcoholic beverage, pharmaceutical, cosmetic, and toiletry industries. According to Ayurveda, the seeds act as a diuretic, antispasmodic, antiepileptic, antispasmodic, antispasmodic, and carminative agent (Tahir et al., 2016; Rebey et al., 2017; Bhatt et al., 2017). According to tradition, the plant can treat a variety of conditions, including diarrhea, jaundice, weight loss, dyspepsia, indigestion, flatulence, hoarseness, toothache, hypertension, scorpion stings, and more (Al-Snafi, 2016; Siow & Gan, 2016; Taghizadeh et al., 2017). Additionally, Indian herbalists frequently recommend cumin for the treatment of fever, colds, and insomnia. To reduce the frequency of upbeats, onion juice and cumin seed paste have also been frequently administered to scorpion and bee stings (Mnif & Afia, 2015). The digesting process is sped up by cumin's stimulation of bile secretion (Srinivasan, 2018). In addition, cumin is used to treat leprosy, kidney and bladder stones, severe diarrhea, and eye conditions. The fruits of Cuminum cyminum are used in the Unani system of medicine to cure corneal opacities, ulcers, boils, styles, and to lessen cough and inflammation (Shivakumar et al., 2010). Cumin paste is used in Indonesia to alleviate rheumatism and prevent bloody diarrhea in addition to reducing headaches (Tahir et al., 2016). According to Tabarsa et al. (2020), the herb is traditionally used in Iran to boost the production of milk, soothe discomfort and flatulence, and act as a potent antispasmodic. It has been demonstrated that it can enhance milk, lessen morning sickness while pregnant, and can be taken as a poultice to treat breast or testicular edema (Jalali-Heravi et al., 2007). Also, some clinical research has been done to back up the ethnopharmacological effects of cumin. Although many of the traditional uses of this herbal formulation still lack adequate scientific validation in terms of safe dose and duration, some of its ethnomedical uses have been scientifically validated.

3.2 Phytochemicals

Cumin seeds include a wide range of nutrients, including a lot of protein, nutritional fiber, and fat. Cumin seeds contain a sizable amount of iron, various dietary minerals, including vitamins B and E, and other minerals. The main Cumin has terpenoids, cuminaldehyde, and cymene as its volatile components; it also has an extremely strong flavor. Due to the presence of essential oils,

it has a warm aroma. Cuminaldehyde and cuminic alcohol make up the majority of its fragrance component composition (Bettaieb et al., 2011). Alkaloids, coumarins, anthraquinones, flavonoids, glycosides, proteins, resins, saponins, tannins, steroids, dietary fibers, minerals, fats (particularly monounsaturated fat), vitamins B (thiamin, vitamin B6, niacin, riboflavin), vitamin A, vitamin C, vitamin E, and other nutrients can be found in abundance in cumin seeds. In addition to these organic acids, cumin seeds also include fumaric, aspartic, citric, malic, tartaric, propionic, ascorbic, oxalic, and maleic acids (Belal et al., 2017). cumin contains volatile oil (3–4%), cuminaldehyde, the main active component, which is present in amounts of 45–50% (Sowbhagya, 2013). The fruits include luteolin, apigenin, and estrogenic isoflavonoids. The seeds contain a healthy amount of flavonoids (4.15–5.75%), the three most prominent of which are luteolin, apigenin, and quercetin (Kang et al., 2019). The substituted pyrazines 2-ethoxy-3-isopropylpyrazine, 2-methoxy-3-sec-butylpyrazine, and 2-methoxy-3-methylpyrazine are additional significant fragrance components of roasted cumin. Safranal, p-cymene, -terpinene, and -pinene are more components (Li & Jiang, 2004).

3.3 Pharmacological effects of Cumin

3.3.1 Antioxidant activity

An antioxidant is defined as a substance that can compete with other oxidizable substrates at low concentrations, preventing their oxidation (Halliwell, 1995). Oxidative stress occurs when, in tissues and organs, the formation of highly reactive molecules e.g., reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS). The reactive species are constantly generated within cells at low concentrations as a result of normal metabolic processes. They can also result from the exposure to external factors like radiation (X-rays and UV), ozone, air pollutants, cigarette smoke, bacteria, viruses, drugs or as the outcome of an acute or chronic cellular stress (Pham-Huy et al., 2008). The intracellular sources of chemical reactive species are mainly mitochondria, endoplasmic reticulum, lysosomes, peroxisomes, cytosol, and plasma membrane (Balaban et al., 2005). ROS derive from the chemical reduction of molecular oxygen and produce free radicals, such as superoxide anion radical ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), as well as non-radical oxidant, such as hydrogen peroxide (H_2O_2) and hypochlorous acid (HClO) (Schieber and Chandel, 2014). Among the RNS, the major players are peroxynitrite radical ($ONOO^-$), ozone, and nitric oxide ($^{\bullet}NO$) (Ray et al., 2012). The new identified RSS

include thiol radical (RS), and RSS both formed by the reaction between ROS and thiols. The most important sites of ROS production are the enzymes of the mitochondrial electron transport respiratory chain. Other enzymes catalyze chemical reactions contributing to the ROS formation, among them the homologs of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, phospholipase A2 (PLA2), uncoupled nitric oxide synthase (NOS) as well as cyclooxygenases (COX), xanthine oxidase (XO), lipoxygenases (LOXs), glucose oxidase, and myeloperoxidase (MPO) (Bhattacharyya et al., 2014; Münzel et al., 2010; Swindle and Metcalfe, 2007).

To establish the profile of cumin antioxidant activity, various studies has reported the scavenger activity of cumin against different reactive species. A study by (Shori, 2020) reported that herbal water extract of dried cumin seeds had a strong anti-oxidant activity, reduce ferric 2,4,6-tripyridyl-s-triazine complex on FRAP assay and improve the radical scavenge ability and increase FIC ability on FIC assay at different concentration 5, 10, 15, & 20 g/100 mL. In vitro study of essential oil extracted from cumin found that at a concentration of 25, 50, 100, & 150 µL, it increases the scavenge ability of DPPH radical on DPPH assay and decrease ferric 2,4,6-tripyridyl-s-triazine complex on FRAP assay (Ghasemi et al.,2019). A study by (El-Ghorab et al.,2010) reported that essential oil of cumin decreases ferric 2,4,6-tripyridyl-s-triazine complex at a dose of 40, 80, 120, 160, 200, & 240 µg/ mL on FRAP assay and also increase scavenge ability of DPPH at same concentration on DPPH assay. The antioxidant capacity of acetone extract of aerial part of cumin by β-Carotene bleaching and DPPH assays was EC_{50} : 53.82±0.02 µg/ mL and IC_{50} : 64.78 ± 0.74 µg/ mL and respectively (Bettaieb et al., 2011). The antioxidant activities of essential oil of cumin were assessed using three tests (FRAP assay, DPPH assay, and β-Carotene bleaching assay) with IC_{50} values of 341.65 ± 0.32 µmol Fe2 + /g, 26.05 ± 0.16 mg/ mL, and 3.04 ± 0.04 µg/ mL, respectively (Ladan Moghadam, 2016). According to (Milan et al., 2008) saline extract of cumin showed antioxidant properties through DPPH assay by increasing Scavenging of DPPH radicals with IC_{50} values of 0.09 ± 0.01 g/ mL. Four assays were used to assess the antioxidant activity of essential oil of cumin: DPPH assay, ABTS assay, OH radical scavenging assay, and FRAP assay with concentration values of (1, 2, 4, & 8 µg/ mL), (2, 4, 6 , & 8 µg/mL), (0.1, 0.2, 0.3, 0.4 , & 0.5 µg/mL), and (5, 10, 20, & 40 µg/mL), respectively (Fang et al., 2018). The effect of cumin oil mediated silver nanoparticle was investigated on DPPH assay. The results showed increased activity of DPPH radical scavenge at a concentration of 2-10 µg/mL (Keerthiga et al., 2019).

Table 1: Summary of antioxidant activity with possible mechanism

Extract/ compounds	Test system(s)/test medium/cell line	Possible mechanism	Conc./dose (admin. route)/ IC_{50}	References
Herbal water extract of dried cumin seeds	Radical scavenging assay	Radical scavenging activity was improved	5, 10, 15, & 20 g/100 mL	Shori, 2020
	FRAP assay	↓ferric 2,4,6-tripyridyl-s-triazine complex		
	FIC assay	↑FIC ability		
Essential oil extracted from cumin	FRAP assay	↓ferric 2,4,6-tripyridyl-s-triazine complex	25, 50, 100, & 150 µL	Ghasemi et al., 2019
	DPPH assay	↑DPPH radical scavenge		
Essential oil of cumin	DPPH assay	Inhibition of DPPH radical	40, 80, 120, 160, 200, & 240 µg/ mL	El-Ghorab et al., 2010
	FRAP assay	↓ferric 2,4,6-tripyridyl-s-triazine complex		
Acetone extract of aerial part of cumin	DPPH assay	Inhibition of DPPH radical	IC_{50} :64.78 ± 0.74 µg/ mL	Bettaieb et al., 2011
	β-Carotene bleaching assay	Slower discoloration of β-carotene	EC_{50} : 53.82±0.02 µg/ mL	
Essential oil of cumin	FRAP assay	↓ferric 2,4,6-tripyridyl-s-triazine complex	IC_{50} :341.65 ± 0.32 µmol Fe^{2+} /g	Ladan Moghadam , 2016
	DPPH assay	↑DPPH radical scavenge	IC_{50} : 26.05 ± 0.16 mg/ mL	
	β-Carotene bleaching assay	Slower discoloration of β-carotene	IC_{50} : 3.04 ± 0.04 µg/ mL	
Saline extract of cumin	DPPH assay	↑DPPH radical scavenge	IC_{50} : 0.09 ± 0.01 g/ mL	Milan et al., 2008

Essential oil of cumin	DPPH assay	Inhibition of DPPH radical	1, 2, 4, & 8 µg/ mL	Fang et al., 2018
	ABTS assay	↑ABTS radical scavenge	2, 4, 6 , & 8 µg/mL	
	OH radical scavenging assay	↓OH radical production	0.1, 0.2, 0.3, 0.4 , & 0.5 µg/mL	
	FRAP assay	↑ FRAP radical scavenge	5, 10, 20, & 40 µg/mL	
Cumin oil mediated silver nanoparticle	DPPH assay	↑DPPH radical scavenge	2-10 µg/mL	Keerthiga et al., 2019
FRAP: ferric reducing antioxidant power assay, DPPH:2,2- diphenyl-1-picrylhydrazyl, ABTS: 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid), FIC: ferrous iron chelating assay				

3.3.2 Anti-inflammatory and Analgesic effects

Inflammation is a common pathogenesis of many chronic diseases, including cardiovascular and bowel diseases, diabetes, arthritis, and cancer pathways impact the pathogenesis of a number of chronic diseases, and involve common inflammatory mediators and regulatory pathways. By producing inflammatory mediators as histamine, serotonin, bradykinin, nitric oxide (NO), interleukin (IL)-1 and IL-6, tumor necrosis factor (TNF)-, and prostaglandins, the inflammation involves cell movement and plasma exudation (Loram et al., 2007). Moreover, the activity of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2), the enzymes involved in the production of NO and PGE- 2, is positively correlated with the expression of pro-inflammatory cytokines (Soufli et al., 2016; Förstermann and Sessa, 2012). According to Henriquez-Olgun et al. (2015), Hendrayani et al. (2016), and Kyriakis et al. (2001), receptor activation activates crucial intracellular signaling pathways such as the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) and nuclear factor kappa-B (NF-B) pathways. Acetic-acid induced writhing, hot plate, and Carrageenan-induced paw oedema methods were used for evaluation of analgesic and anti-inflammatory effects of ethanolic extracts. The study demonstrates that extract (200 mg/kg, and 500 mg/kg p.o.) decreased release of serotonin, histamine, bradykinin, and prostaglandins and decreased the release of cyclooxygenase as well

in Swiss Albino mice and decrease NO production, opioid-like effect and inhibitory action on the release of prostaglandinsin in Rats of either sex (Bhat et al., 2014). A study by (Golabi et al., 2022) reported that cumin extract and cumin -AuNPs had a strong anti-inflammatory and anti-nociceptive activity on Male Wistar rats (Formalin test) to decrease the release of serotonin, histamine, bradykinin, and prostaglandins and inhibit the release of cyclooxygenase at a concentration of 200, 500, and 1000 mg/kg. Another study investigated that essential oil of cumin inhibit nociception by decreasing the release of cyclooxygenase with IC_{50} value 1.8 ± 0.41 µg/mL (Alomar et al., 2022).

Table 2: Summary of anti-inflammatory and analgesic effects with possible mechanism

Extract/ compounds	**Test system(s)/test medium/cell line**	**Possible mechanism(s)**	**Conc./dose (admin. route)/ IC_{50}**	**References**
Ethanolic extracts of Cumin seeds	Swiss Albino mice (Acetic-acid Induced Writhing) (n=6)	↓release of serotonin, histamine, bradykinin, and prostaglandins; ↓release of cyclooxygenase	200 mg/kg p.o. and 500 mg/kg p.o.	Bhat et al., 2014
	Rats of either sex (Eddy's Hot Plate) (n=6)	↓NO production and opioid-like effect	200 mg/kg p.o. and 500 mg/kg p.o.	
	Rats of either sex (Carrageenan-induced Paw Oedema) (n=6)	Inhibitory action on the release of prostaglandins	200 mg/kg p.o. and 500 mg/kg p.o.	

Essential oil of cumin	Anti-inflammatory assay	↓release of cyclooxygenase	IC50 = 1.8 ± 0.41 µg/mL	Alomar et al., 2022
Cuminaldehyde obtained from cumin seeds	Male albino NMRI mice (Formalin test) (n=3)	Suppression of inflammatory cytokines	50, 100, and 200 mg/kg	Koohsari et al., 2020
	Male albino NMRI mice (Hot plate test) (n=3)	Stimulation of opioid receptors		
	Male albino NMRI mice (Acetic acid-induced writhing test) (n=3)	↓NO production		
Cumin extract and cumin - AuNPs	Male Wistar rats (Formalin test) (n=3)	↓release of serotonin, histamine, bradykinin, and prostaglandins; ↓release of cyclooxygenase	200, 500, and 1000 mg/kg	Golabi et al., 2022

3.3.3 Antimicrobial effects

Methanolic cumin extract was tested for antimicrobial activity in vitro well diffusion method. Methanolic cumin extract exhibited antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* (Kulkarni et al., 2014). An in vitro study by (Bouhenni et al., 2019) reported methanolic cumin seed extract had a strong antibacterial activity against *S. aureus, E. coli* and *B. subtilis* at a concentration of 50 and 100 mg/ml, zones of inhibition for cumin using the disc-diffusion approach were 21 mm, 12 mm, and 18 mm, respectively for *S. aureus, E. coli*

and *B. subtilis*. The extracted oils from seeds of cumin, exerted antibacterial activity against *Staph. aureus, E. coli, P.aeruginosa, Klebsiella* sp with inhibition zone 37-45 mm using well-diffusion method (Jabbar, 2013).In vitro Mueller Hinton Agar medium was used to identify the antibacterial activity of methanolic extract of cumin with zone of inhibition ranged from 18-36 mm against *Salmonella typhi, Pseudomonas aeruginosa, Staphylococcus aurous,* and *Escherichia coli* (Akbar et al., 2019). Belal et al., 2017 used Gram-negative (*E. Coli, S. Typhi*) and gram-positive (*P. Vulgaris, K. Pneumonae, E. Feacalis* and *S. aureus)* bacterial strains to assess anti-bacterial activity by cup-plate agar diffusion method The inhibitory effect of essential oil of cumin was tested against *S. typhimurium, E. coli* and *S. aureus* in disc diffusion method with showed significance zone of inhibition. The results showed that cumin oils possessed strong antibacterial activity (Bisht et al., 2014). Ethanolic cumin extract at a concentration 50,100 and 200 µg/ml showed antimicrobial activity against *E. coli, P. aeruginosa, S. agalactiae, S. aureus* studied by Ameneh et al.,2018.

The antifungal activities of the essential oils obtained against Aspergillus flavus, Candida albicans, Cryptococcus sp in Sabouraud Dextrose agar medium. Different concentrations of the essential oils (0.95 ,0.85 ,0.75 ,0.65 ,0.6 ,0.55 , 0.45 ,0.35 ,0.1 ,0.04 ml/ml) exhibited remarkable inhibition with ZOI ranged from19–22 mm (Jabbar, 2013). The effect of different concentrations of Cumin essential oil (250, 500, 750, 1000 and 1500 µL L^{-1}) was studied on growth of *Botrytis cinerea, Aspergillus niger* and *Penicillim expansum* in potato dextrose agar medium. The study demonstrated that essential oil of cumin showed antifungal effects by disrupt the permeability barrier of cell membrane and prevents respiration (Ghasemi et al., 2019). The essential oil from *Cuminum cyminum* was investigated for its in vitro antifungal properties against *C. glabrata, C. albicans, C. krusei, C. parapsilosis, and C. dubliniensis.* Inhibition zone values were ranged from 7 to 50mm against the tested organisms. The best minimal inhibitory concentration (MIC) of Cuminum cyminum oil was recorded against *C. albicans and C. dubliniensis* (289 mg/l) (Naeini et al., 2014). Methanolic cumin extract induced mild antifungal effect against Candida albicans in vitro with significance inhibition zone (Kulkarni et al., 2014).

Table 3: Summary of antimicrobial effects with possible mechanism

Extract/ compounds	Test system(s)/test medium/cell line	Possible mechanism(s)	Conc./dose (admin. route)/ IC_{50}	References
Antibacterial effects				
Methanolic cumin extract	(*Escherichia coli, Staphylococcus aureus*) well diffusion method; in vitro	Significant inhibition with ZOI ranged from 5–15 mm	1gm cumin powder per 10ml of 80% methanol (10µl-50µl)	Kulkarni et al., 2014
Methanolic cumin seed extract	(*S. aureus, E. coli* and *B. subtilis*) Disc-diffusion methods; in vitro	Cumin has a 21 mm, 12 mm, and 18 mm diameter zone of inhibition for *S. aureus, E. coli,* and *B. subtilis,* correspondingly.	(50 and 100 mg/ml)	Bouhenni et al., 2019
Extracted oil of cumin	*Staph. aureus, E. coli, P. aeruginosa, Klebsiella sp* (Well-diffusion method)	Inhibition zone: 37-45 mm	0.95 ,0.85 ,0.75 ,0.65 ,0.6 ,0.55, 0.45 ,0.35 ,0.1 ,0.04 ml/ml	Jabbar, 2013
Methanolic cumin seed extract	*Salmonella typhi, Pseudomonas aeruginosa, Staphylococcus aurous* and *Escherichia coli* (Mueller Hinton Agar medium)	Significant inhibition with ZOI ranged from 18–36 mm	100µL	Akbar et al., 2019

Essential oil of cumin	*S. typhimurium* and *E. coli* (Disc diffusion method)	Zone of inhibition 22 mm and 17 mm against S. typhimurium and E. coli respectively	10 µL and 5 µL	Bisht et al., 2014
Ethanolic cumin extract	*E. coli, P. aeruginosa, S. agalactiae, S. aureus* (Disc diffusion method)	Zone of inhibition: 8–19 mm	50,100 and 200 µg/ml	Ameneh et al., 2018
Antifungal effects				
Methanolic cumin extract	Fungal strains: (*Candida albicans*) well diffusion method; in vitro	Remarkable inhibition with ZOI ranged from10–20 mm	1gm cumin powder per 10ml of 80% methanol (10µl-50µL)	Kulkarni et al., 2014
Essential oil of cumin	*Aspergillus niger, Penicillium expansum, and Botrytis cinerea* potato dextrose agar medium)	Disrupt the permeability barrier of cell membrane and prevent respiration	250, 500, 750, 1000 and 1500 µL L^{-1}	Ghasemi et al., 2019
Extracted oil of cumin	*Aspergillus flavus, Candida albicans, Cryptococcus* sp. (Sabouraud Dextrose agar medium)	Remarkable inhibition with ZOI ranged from19–22 mm	0.95 ,0.85 ,0.75 ,0.65 ,0.6 ,0.55 , 0.45 ,0.35 ,0.1 ,0.04 ml/ml	Jabbar, 2013

Essential oil of cumin	*C. albicans, C. dubliniensis, C. glabrata, C. krusei and C. parapsilosis* (Agar disc diffusion method)	Diameter zone of inhibition: 7–50 mm	40 µL	Naeini et al., 2014

3.3.4 Anti-cancer activity

Anticancer effect of nanogel containing cumin essential oil at a concentration of 62.5, 125, 250, 500, and 1000 µg/mL against A-375 cells in MTT assay. This study has been shown chemo-preventive potential by decreasing cell viability (Ranjbar et al., 2023). A study carried by Perumal, (2023) to evaluate the anticancer propertied of cumin extract at a dose of 10-100µg/ml. This study exhibit shrinkage and cytoplasmic membrane blebbing on HT-116 cell line in MTT assay. In SRB assay the compound [1-(2-Ethyl, 6-Heptyl) Phenol] from cumin had showed chemo- preventive potential against (HEPG2; HELA; HCT116; CACO2; MCF7; HEP2) cell lines by interacting with DNA by intercalation and inhibiting the activity of topoisomerase at the dose of 1, 2.5, 5 and 10 µg/ml (Mekawey et al., 2009).

Table 4: Summary of anti-cancer activity with possible mechanism

Extract/ compounds	**Test system(s)/test medium/cell line**	**Possible mechanism(s)**	**Conc./dose (admin. route)/ IC_{50}**	**References**
Nanogel Containing cumin essential oil	A-375 cells (MTT assay)	Cell viability after treatment with nanogel was decreased	62.5, 125, 250, 500, and 1000 µg/mL	Ranjbar et al., 2023

Cumin extract	HT-116 cell (MTT assay)	Exhibit shrinkage and cytoplasmic membrane blebbing	10-100µg/ml	Perumal, 2023
[1-(2-Ethyl, 6-Heptyl) Phenol] from Cumin seeds	HEPG2; HELA; HCT116; CACO2; MCF7; HEP2 (SRB Assay)	Interact with DNA by intercalation; topoisomerase inhibitors	1, 2.5, 5 and 10 µg/ml	Mekawey et al., 2009
SRB: Sulphorhodamine B, ; MTT: 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide				

3.3.5 Antidiabetic effects

Tahir et al., 2016 carried out α-amylase assay at a concentration of (1 to 100 µg/mL) of cumin essential oil and emulsion when showed hypoglycemic effect by inhibiting α-amylase activity. The antidiabetic effects of ethanolic cumin extract, was examined in streptozotocin induced diabetic rats. In diabetic rats, this was accompanied by a drop in circulating glucose levels and an increase in insulin levels at a concentration of 200 mg/kg body weight (Mohamed et al., 2018). At a concentration of 0.25 g kg^{-1} cumin powder was studied in alloxan diabetic rats. This treatment resulted in a significant reduction of blood glucose level; by potentiating the insulin effect and increase pancreatic secretion of insulin (Dhandapani et al., 2002). The orally administered methanolic extract of cumin seeds (200, 400 and 600 mg/kg) lowered the blood glucose levels in streptozotocin induced diabetic rats. Reduced elevated blood glucose, increased serum insulin, and increased glycogen content resultant this antidiabetic effect.

Table 5: Summary of antidiabetic effects with possible mechanism

Extract/ compounds	**Test medium/ cell line/test system**	**Possible mechanism(s)**	**Conc./dose (admin. route)/ IC_{50}**	**References**
Cumin essential oils and emulsions	α-amylase assay	Inhibit α-amylase activity	1 to 100 µg/mL	Tahir et al., 2016
Ethanolic cumin extract	Male albino rats(streptozotocin induced type 2 diabetes)	Reduced plasma glucose levels in diabetic rats; elevate insulin levels	200 mg/kg	Mohamed et al., 2018
Methanolic extract of cumin seeds	Adult Wistar rats(streptozotocin induced diabetes)	Reduced elevated blood glucose; increased serum insulin; increased glycogen content	200, 400 and 600 mg/kg	Jagtap and Patil, 2010
Cumin powder	Female albino Wistar rats(alloxan induced diabetes)	Potentiating the insulin effect; increase pancreatic secretion of insulin	0.25 g kg^{-1}	Dhandapani et al., 2002

3.3.6 Effects on CNS

The pathophysiology of convulsion remains ambiguous. Convulsions may be caused by epileptic seizures, febrile seizures, non-epileptic seizures, or paroxysmal kinesigenic dyskinesia (Grattan-Smith, P. 2011). Convulsion has been produced by inhibiting γ-aminobutyric acid (GABA) neurotransmission (Löscher & Schmidt, 2006). GABA is the main inhibitory neurotransmitter substance in the brain, and is widely implicated in epilepsy. Enhancement of GABAergic neurotransmission has been shown to inhibit or attenuate convulsion, while its inhibition or activity is known to promote and facilitate convulsion (Smith et al., 2007) $GABA_A$ receptor antagonist, produces seizures by blocking the chloride-ion channels linked to $GABA_A$-receptors, thus preventing the entry of chloride ions into the brain and, consequently, inhibitory transmission in the brain (Löscher & Schmidt, 2006). Depression (major depressive disorder) is a common and serious medical illness that is produced by orticotropin-releasing hormone (CRH) (Young, 1998), and depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system. Serotonin is the most extensively studied neurotransmitter in depression (Neumeister et al., 2002).

Various study demonstrate that cumin has strong neuroprotective activity. At the concentration of 100, 200, and 300mg/kg, aqueous cumin extract increase urinary VMA excretion on Wistar rats and prevent stress and depression (Koppula and Choi, 2011). Another study investigated by Janahmadi et al., (2006) reported that essential oil of cumin decreased firing rate of F1 neuronal soma membrane, and reduction of the amplitude of AHP at a dose of 1% and 3% of essential oil. Pentylenetetrazole induced epilepsy on Helix aspersa (Iranian garden snail) was reduced by suppression of epilepcy.

Table 6: Summary of CNS effects with possible mechanism

Extract/ compounds	**Test medium/ cell line/test system**	**Possible mechanism(s)**	**Conc./dose (admin. route)/ IC_{50}**	**References**
Aqueous cumin extract	Wistar rats (forced swimming method)	Increase urinary VMA excretion	100, 200, and 300mg/kg	Koppula and Choi, 2011

Essential oil of cumin	Helix aspersa (Iranian garden snail) (PTZ induced epilepsy)	Suppressed excitability; Decreased firing rate of F1 neuronal soma membrane; reduction of the amplitude of AHP	1% and 3% of essential oil	Janahmadi et al., 2006
PTZ: pentylenetetrazole, GABA: γ-aminobutyric acid, nAChR: nicotinic acetylcholine receptor, $GABA_AR$: γ-aminobutyric acid A receptor				

3.3.7 Hepatoprotective effects

Various studies demonstrate that cumin has strong hepatoprotective effects. The hepatoprotective activity of ethanolic cumin extract was studied against cisplatin induced hepatotoxicity on albino mice. 150mg/kg of extract was administered orally which provided decreasing at the concentrations of ALT, AST, and ALP, raising the amounts of TPC, increased the level catalase, superoxide dismutase, and glutathione (Abbas et al., 2017). Another study investigated by Ebada, (2018) reported that essential oil of cumin normalized acetaminophen induced liver enzymes elevation at a dose of 400 mg/kg in male Wistar rats which act as hepatoprotective agent. Studies proved that antihepatotoxic activity of cumin extract at a concentration of 100 mg/kg body weight using Profenofos induced liver toxicity in female Swiss albino mice. Cumin extract was found to show hepatoprotective effect by decreasing the activities of serum transaminases and restoring the normal SGPT and SGOT levels (Kumar et al., 2011). Hepatoprotective activity of cumin seeds powder was investigated by inducing hepatotoxicity with acetaminophen in male Wistar rats. The powder at a dose of (200 mg/kg, 400 mg/kg, and 800 mg/kg) body wt. exhibited orally, significant protective effect by decreasing serum ALT & AST and decreasing levels of H_2O_2 and MDA as well (Mozaffarinia et al., 2023).

Table 7: Summary of hepatoprotective effects with possible mechanism

Extract/ compounds	**Test medium/ cell line/test system**	**Possible mechanism(s)**	**Conc./dose (admin. route)/ IC_{50}**	**References**
Ethanolic cumin extract	Albino mice (cisplatin induced hepatotoxicity)	reduced ALT, AST, and ALP concentrations; elevated the level of TPC; increased the level catalase, superoxide dismutase and glutathione	150mg/kg orally	Abbas et al., 2017
Cumin extract	female swiss albino mice (Profenofos Induced Liver Toxicity)	decreased activities of serum transaminases; restores the normal SGPT and SGOT levels	100 mg/kg b.w	Kumar et al., 2011
Essential oils of green cumin	male Wistar rats(acetaminophen induced hepatotoxicity)	normalized acetaminophen induced liver enzymes elevation	400 mg/kg	Ebada, 2018

Cumin Seeds Powder	male Wistar rats(acetaminophen induced injury)	Decreased serum ALT & AST; Decreased levels of H2O2 and MDA	200 mg/kg ,400 mg/kg and 800 mg/kg	Mozaffarinia et al., 2023
ALT: alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; SGPT: Serum Glutamic Pyruvic Transaminase; SGOT: serum glutamic-oxaloacetic transaminase				

3.3.8 Other effects

3.3.8.1 Anti-osteoporotic effect

The anti-osteoporotic activity of Cuminum cyminum was evaluated in rats. Adult Sprague-Dawley rats were bilaterally ovariectomized (OVX) and and randomly assigned to groups. Administration of 1 g/kg of methanolic extract of cumin in two divided doses for 10 weeks. At the end of the study blood, bones and uteri of the animals were collected. Cumin extract reduced urinary calcium excretion as a result higher calcium content in bone which increased the mechanical strength of bones (Shirke et al., 2008).

3.3.8.2 Gastrointestinal effect

The Gastrointestinal effect of the cumin seeds extract against the absolute ethanol induced stomach ulceration has been studied in rats male adult rats at a dose of 250, 500 and 800 mg/kg. Cumin extract accelerated the healing process to different extents mainly by increasing the level of pH of the gastric environment and mucus production (Alkubaisy et al., 2019).

3.3.8.3 Protective effect against nephrotoxicity

This study was done by using aqueous extract of cumin (100 and 200 mg/kg) administered in male albino rats. In this study gentamicin was used, to induce nephrotoxicity in rats. The results showed that cumin was effective in decreasing the level of serum urea and creatinine, and increasing renal clearance (CM et al., 2010).

Table 8: Anti-osteoporotic effect, gastrointestinal effect and protective effect against nephrotoxicity with possible mechanism

Extract/ compounds	**Test medium/ cell line/test system**	**Possible mechanism(s)**	**Conc./dose (admin. route)/ IC_{50}**	**References**
Anti-osteoporotic effect				
Methanolic Extract of Cumin	female Sprague-Dawley rats(ovariectomy induced bone loss)	lowered calcium outflow through the urine; raised bone calcium content and rigidity	0.5 and 1 g/kg, administered orally for 6 weeks	Shirke et al., 2008
Gastrointestinal effect				
Cumin seeds extract	male adult rats (Gastric Ulcer-Induction by Absolute Ethanol)	Formation of mucus and an elevated pH of the stomach	250, 500 and 800 mg/kg	Alkubaisy et al., 2019
Protective effect against nephrotoxicity				
Aqueous extract of Cumin	Male albino rats (gentamicin induced nephrotoxicity)	Renal clearance enhanced and lipid peroxidation, serum urea, and creatinine levels dropped	100 and 200 mg/kg	CM et al., 2010

CHAPTER FOUR

CONCLUSION

4. Conclusion

Cumin (*C. cyminum L.*) contains a wide range of phytochemicals including alkaloids, coumarins, anthraquinones, flavonoids, glycosides, proteins, resins, saponins, tannins, steroids etc. which are responsible for different biological activities, anti-inflammatory, analgesic, antibacterial, antidiabetic, anticancer, hepatoprotective, gastrointestinal, and anti-osteoporotic properties. Numerous research conducted over the past few decades support that it has a beneficial effect on health, especially in the plant can treat a variety of conditions, including diarrhea, jaundice, weight loss, dyspepsia, indigestion, flatulence, hoarseness, toothache, hypertension, scorpion stings, and more. Therefore, this study comes to the conclusion that cumin has a variety of pharmacological potential and health advantages in addition to its usage as a flavoring ingredient. Further study is required to fully comprehend crucial issues such as the isolation of significant phytocompounds, pre-clinical trials, clinical identification, assessment, and the structure activity relationship.

CHAPTER FIVE

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