FORMULATION AND EVALUATION OF HERBAL TABLET OF CURCUMIN FOR ANTICANCER ACTIVITY

1Miss. Shalini R. Patle, 2Dr. Rajesh Z. Mujariya
1M.pharm Student, 2Principal And Director
1Institute of Pharmaceutical Science And Research, 2Institute of Pharmaceutical Science And Research

Abstract:
This thesis examines the effectiveness of curcumin against breast cancer and provides a compelling case for their value as cancer preventatives.

Given that free radicals are primary factor behind the occurrence of cancer, phytochemical analysis of the chosen plant reveals the presence of flavonoids, which have strong antioxidant activity and are also known to be useful in treating malignant development. Curcumin and its analogous compounds, such as eugenol, eugenol orthodimer (also known as bis-eugenol or 3,3'-dimethoxy-5,5'-di-2-propenyl-1,1'-biphenyl-2,2'-diol), and isoeugenol, were examined to assess their impact on cell toxicity, ability to generate reactive oxygen species (ROS), and capacity to scavenge radicals. This article discusses the properties of curcumin, a yellow pigment present in the rhizome of the Curcuma longa plant. Curcumin has been extensively researched due to its various biological impacts, such as anti-inflammatory and antioxidant properties. The article delves into the underlying biological mechanisms and potential therapeutic benefits of utilizing curcumin as a treatment in cancer therapy. A natural substance with excellent therapeutic potential is curcumin. Numerous studies have demonstrated the wide range of biological activities of curcumin, one of which is its potent anti-inflammatory properties. A physiological and pathological process that is both complex and widespread is inflammation.

A tablet is a unit solid dose form that includes the active drug, together with any necessary excipients. These dose forms are the most often utilized. The primary objective in the design and manufacturing of compressed tablets is to provide precise oral dosages of medication in the appropriate form, timing, and location, while safeguarding the chemical integrity of the drug at its targeted site of action. The efficacy of the administered drug can be notably...
influenced by factors such as the tablet's physical arrangement, production process, and overall chemical makeup. Nearly 40% of the novel chemical entities being discovered at this time are poorly water-soluble medicines, which are linked to sluggish drug absorption and eventual inadequate and variable bioavailability.

**Keywords:** Curcumin, Cytotoxicity, ROS (reactive oxygen species), Cancer, Curcuma Longa, Tablet.

1. **INTRODUCTION**

1.1 **CURCUMIN:**

The primary component within turmeric, referred to as curcumin (scientifically known as diferuloylmethane), originates from the underground stem of the East Indian plant Curcuma longa. Curcuma longa, a perennial plant belonging to the ginger family (Zingiberaceae), is native to Southeast Asia. Within turmeric, there exist curcuminoids, a group of substances which encompass curcumin, desmethoxycurcumin, and bisdemethoxycurcumin. Among these, curcumin, the principal curcuminoid, constitutes approximately 2-5% of turmeric, responsible for both the spice's distinct yellow hue and a substantial portion of its medicinal properties. Beyond its role as a food enhancer and colorant, turmeric has a rich history of use in Ayurvedic medicine due to its recognized antioxidant, antibacterial, pain-relieving, antimalarial, and anti-inflammatory characteristics. Curcumin has been employed as a dietary supplement since ancient times, and it is widely regarded as having a favorable safety profile from a pharmacological perspective.[1]

![Molecular Structures of Curcumin, Demethoxycurcumin, and Bis-Demethoxycurcumin](image)

**Figure 1.1** illustrates the molecular structures of Curcumin, Desmethoxycurcumin, and Bis-Demethoxycurcumin.
Plants or biometabolites include a number of substances similar to curcumin. The unprocessed drug "Turmeric" contains curcuminoids like curcumin, monodemethoxycurcumin, and bisdemethoxycurcumin. It is well known that the active metabolite of curcumin is tetrahydrcocurcumin (THC).[2]

1.2 Anti-Cancer plants:
The use of natural products, particularly plants, for medicinal purposes has a rich history that spans across different cultures and civilizations. For thousands of years, terrestrial plants have been employed as remedies in various societies, including ancient Egypt, China, India, and Greece. Many modern pharmaceuticals have their origins in plant-based compounds. The earliest documented evidence of the therapeutic use of plants dates back to around 2600 BC, with records from the Sumerians and Akkadians. One of the most well-known historical documents related to herbal medicine is the "Ebers Papyrus," an Egyptian text that contains information about more than 700 medicinal substances. This document provides insights into the practice of Egyptian medicine dating back to 1500 BC. Similarly, the Chinese Materia Medica, which catalogs over 600 medicinal plants, has a documented history dating back to around 1100 BC. In India, Ayurvedic medicine has a long tradition of using herbal remedies. Knowledge of Ayurvedic formulations and principles has been recorded in texts like those from the Susruta and Charaka periods, dating back to about 1000 BC. The ancient Greeks also made significant contributions to the field of herbal medicine. Dioscorides, a Greek physician who lived around 100 A.D., authored a work titled "De Materia Medica," which detailed the uses of more than 600 medicinal plants. This work is considered one of the foundational texts in the history of herbal medicine. Throughout history, these various cultures have documented their knowledge of medicinal plants and their applications. These records have served as valuable resources for the development of modern medicine and pharmaceuticals. The use of plants as a source of therapeutic agents continues to be an area of interest and research, with many natural products forming the basis for new drugs and treatments.[3] Phytochemicals have been projected for proposal shield against an assortment of chronic diseases that involve obesity, cardiovascular diseases, diabetes, and malignancy. With respect to malignancy assurance, it has been evaluated that nutrition contain variety of phytochemicals can diminish disease hazard by 20%. The constituents that are answerable for therapeutic characteristics of the drug are commonly secondary metabolites. Science behind natural product has assumed a functioning job in producing countless medication in a drug research regimen. Currently, that around 49 % of 877 compounds that were presented as new pharmaceuticals somewhere in the range of 1981 and 2002 by New Chemicals Entities were either natural compounds or their derivatives or synthetic or semisynthetic or synthetic grounded on natural invention models.[4]
Turmeric (Curcuma longa) is a flowering plant belonging to the Zingiberaceae family, which is also known as the ginger family. It is primarily cultivated for its rhizomes, which are used for various purposes, including culinary and medicinal applications. The plant is native to the Indian subcontinent and Southeast Asia. Turmeric is a perennial herbaceous plant that grows from rhizomes, which are underground stem structures. These rhizomes are the part of the plant that is harvested and used. Turmeric requires specific climatic conditions to grow well. It thrives in temperatures ranging from 20 to 30 °C (68 to 86 °F) and requires a substantial amount of annual rainfall to support its growth. The bright yellow or orange pigment of turmeric is due to a compound called curcumin, which also contributes to its various health benefits. In addition to its use as a spice in cooking, turmeric has been traditionally used in Ayurvedic and traditional medicine for its potential health-promoting properties. The rhizomes of the turmeric plant are typically harvested, dried, and ground to produce the vibrant yellow powder that is commonly used in cooking to add flavor and color to dishes. Beyond its culinary uses, turmeric has gained attention for its potential medicinal properties, including anti-inflammatory and antioxidant effects.

**TAXONOMY:**

- **Scientific Name:** Curcuma Longa
- **Family:** Zingiberaceae
- **Kingdom:** Plantae
- **Sub-Kingdom:** Tracheobionta-Vascular plants
- **Order:** Zingiberals
- **Super-division:** Spermatophyta
- **Division:** Magnoliophyta- Flowering plants
- **Class:** Liliopsida- monocotyledons
- **Sub-class:** Zingiberidae
- **Genus:** Curcuma L. curcuma
- **Species:** Curcuma longa L
- **Synonym:** Diferuloylmethane

**Used:** Leaf, Root and Bark Flower.
Figure 1.2 Chemical Structure of Curcumin[8]

Synonyms:[9]


Uses[10]:

a) Natural antioxidant curcumin has anti-inflammatory properties.

b) A number of cancers can be treated and prevented with its help.

c) It is a long-term therapeutic choice for osteoarthritis patients that is secure and productive.

d) Curcumin has been found to increase the levels of brain-derived neurotrophic factor (BDNF). BDNF is a crucial protein that supports the growth, survival, and function of neurons in the brain.

e) Curcumin has demonstrated positive effects on several factors that are associated with heart disease. It is known to have anti-inflammatory, antioxidant, and anti-thrombotic properties.

f) Joint inflammation is a typical feature of the condition known as arthritis. There is a growing body of research that suggests the potential effectiveness of curcumin in treating the signs and symptoms of.
arthritis.

g) The most popular uses for turmeric are as a cosmetic ingredient, in dietary supplements, as a food flavoring (such as in the South and Southeast Asian beverages with turmeric flavoring), and as a food colouring (such as in curry powders, mustards, butters, and cheeses).

h) The active compound found in turmeric, curcumin, is indeed used as a food additive to provide an orange-yellow coloring to prepared foods. In the European Union, it is assigned the E number E100, which is a classification for food additives permitted for use in the EU.

i) Additionally, it has FDA approval to be used as food colouring in the US.

1.3 General Information and History:

Cancer, the second most life-threatening condition, stands as a significant global public health challenge. In 2018 alone, approximately 1.73 million new cancer cases were diagnosed, leading to over 609,000 cancer-related deaths in the United States. Despite notable advancements in cancer treatment, both the reported incidence and mortality rates have not shown improvement over the past three decades. A crucial aspect of cancer prevention and management lies in comprehending the molecular changes driving cancer growth and progression. By specifically targeting cancer cells, it's possible to impede tumor growth, progression, and metastasis without causing detrimental side effects. Numerous anticancer compounds with diverse mechanisms of action have been identified from plant sources such as Taxus brevifolia, Catharanthus roseus, Betula alba, Cephalotaxus species, Erythroxylum previllei, and Curcuma longa, in addition to chemically synthesized anticancer drugs. Among these, curcumin, first isolated from Curcuma longa L. (turmeric) in 1870, holds particular significance. With its biofunctional properties including anti-tumor, antioxidant, and anti-inflammatory actions, curcumin and its derivatives have garnered significant attention in recent decades. These beneficial characteristics stem from the essential components within the curcumin molecule. Hence, scientific research has diligently explored the structure-activity relationship (SAR) of curcumin to enhance its physicochemical and biological attributes. This review primarily centers on curcumin’s anticancer activity, acknowledging the gravity of cancer as a leading cause of mortality and the ongoing quest for more efficacious and less harmful anticancer treatments. The scope of this review does not encompass curcumin's applications in various illnesses, which have been addressed elsewhere.[111] Curcumin’s distinctive anticancer effectiveness is predominantly achieved through two main mechanisms: inducing apoptosis and hindering tumor growth and invasion via the inhibition of several cellular signaling pathways. Various studies have demonstrated curcumin’s anticancer potential across an array of cancer cell lines, including those associated with breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumors. However, despite its numerous advantages, curcumin faces limitations.[12] Its low water solubility negatively affects oral bioavailability and chemical stability. Additionally, curcumin exhibits low cellular absorption due to its
hydrophobic nature, limiting its availability within the cytoplasm. To address these challenges and enhance overall anticancer efficacy, structural modifications have been proposed for curcumin to increase selective toxicity towards specific cancer cells, improve bioavailability, and boost stability. Utilizing diverse delivery methods is another strategy to enhance curcumin’s physicochemical attributes and anticancer potential. This study’s primary focus revolves around contemporary research into the SAR of curcumin and its analogues, their anticancer effects in various cancer cell lines, animal models, and human clinical trials, as well as the numerous delivery systems employed to enhance curcumin's anticancer properties.

The natural substance curcumin, which belongs to the diarylheptanoid class of substances known as curcuminoids, is derived from the underground stem of the East Indian plant Curcuma longa L., commonly referred to as turmeric. Desmethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin are the other three main curcuminoids found in turmeric; collectively, they are referred to as the curcuminoid complex. In traditional Asian medicine, the turmeric plant and the remedies derived from it boast an extensive history of therapeutic utilization. The unprocessed, frequently dried plant material is commonly used as a food component in curry spices, which frequently also include a variety of additional substances. Additionally, Turmeric and its derivatives hold a prolonged legacy of being employed as dietary supplements and herbal remedies, chiefly to address a range of inflammatory conditions. Notably, curcumin has been demonstrated to have a variety of pharmacological effects, and more than 40 years of scientific study have demonstrated both its exhibit potential as a potential therapeutic agent for numerous chronic conditions and display chemopreventive properties. Despite its scientific history spanning nearly two centuries, curcumin consistently attracts researchers from across the globe. Following its initial extraction from turmeric in 1815, there were very few publications on its chemical makeup, production, and biochemical and antioxidant activities until the 1970s. However, the speed of curcumin study has accelerated since the 1990s article by Aggarwal and colleagues on its possible anticancer effect, with a current count of over 14,000 citations. Although a significant portion of studies have concentrated on its biological attributes, a handful of others have been drawn to the crucial chemistry of curcumin that underlies its distinct biological action. For chemists working in span various domains of chemistry, encompassing organic, inorganic, physical, and analytical chemistry, curcumin research has emerged as one of their most popular topics. The primary focus of research in organic chemistry revolved around the extraction and synthesis of curcumin, as well as the creation of innovative synthetic compounds. In the realm of inorganic chemistry, emphasis was placed on the exploration of the -diketo group, which have harnessed its metal chelating properties to create novel structural entities with altered biological functions. To investigate curcumin’s investigated its interactions with micro heterogeneous systems and biomolecules. Physical chemists have delved into the behavior of curcumin and its -diketo group in these contexts, studying factors such as concentrated on its incredibly sensitive spectroscopic characteristics. Chemistry research has also explored the chemical reactivity of curcumin concerning reactive oxygen species (ROS), addition reactions,
degradation processes, and the formation of nanoconjugates and formulations. These investigations have contributed to comprehending the biological effects of curcumin. The present publication focuses on selected noteworthy recent advancements in curcumin chemistry, particularly those relevant to its potential for developing curcumin-based medications. This selection is mindful of the extensive volume of reviews covering diverse aspects of curcumin-related fields. There is a lot of misunderstanding regarding what curcumin means in the scientific and biomedical journals as well as in public literature. As a result, one group created the classification system that is detailed below.

As a nutritional supplement, curcumin is offered by numerous businesses. Dietary supplements are controlled as foods, not pharmaceuticals, in the United States. Therefore, In cases where explicit claims for disease prevention or treatment are not asserted, premarket evaluation and approval from the U.S. Food and Drug Administration (FDA) are not required. Dietary supplements that are judged dangerous by the FDA may be taken off the market. Ingredients in dietary supplements may differ significantly from lot to lot because manufacturing consistency is not regularly reviewed for them. Furthermore, there is no assurance that the components listed on product labels, it is indeed necessary to ensure that the claims or stated quantities are accurate and truthful. Curcumin use as a cancer or other medical condition treatment has not received FDA approval.

1.4 Structural Characteristics of Curcumin:

The chemical compound curcumin, also known as diferuloyl methane, exhibits symmetry. It is assigned the IUPAC nomenclature (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl). 1,6-Heptadiene-3,5-Dione, possessing a molecular weight of 368.38 and the chemical formula C21H20O6. Its structure comprises three distinct chemical components: two aromatic ring systems with o-methoxy phenolic groups connected by a seven-carbon linker constituted by an α,β-unsaturated β-diketone moiety. The chemical arrangement of curcumin is depicted. The diketo group can undergo keto-enol tautomerism, yielding various conformers influenced by the environment. In its cis-enol configuration within the crystal, the structure comprises three substituted planar groups interconnected by two double bonds, stabilized by resonance-assisted hydrogen bonding. The enol form is generally 5 to 8 kcals/mol more stable than the keto form in most non-polar and moderately polar solvents, depending on solvent characteristics. The extended conjugation leads to electron cloud distribution across the molecule. In the trans-form, the two phenolic-methoxy groups are positioned on opposing sides of the curcumin backbone. This form exists in solution as cis-trans isomers, with the trans-form being marginally more stable than the cis-form, where the groups are situated on the same side. Curcumin in its ground state exhibits a calculated dipole moment of 10.77 D. With a logP value of 3.0, curcumin is hydrophobic in nature. It exhibits low solubility in water but is soluble in polar solvents such as DMSO, methanol, ethanol, acetonitrile, chloroform, and ethyl acetate. In hydrocarbon solvents like cyclohexane and hexane, its solubility is weak. Curcumin’s spectral characteristics reveal two distinct absorption bands: one in the visible range with a peak between 410 and 430 nm, and another in the UV range with a peak
at 265 nm. In methanol, its molar extinction coefficient at 425 nm is 55,000 dm$^3$ mol$^{-1}$ cm$^{-1}$. Considering that curcumin has three labile protons and acts as a weak Brönsted acid, three pKa values are estimated, corresponding to three prototropic equilibria. These pKa values are determined through absorption spectrometry and NMR. At the first pKa within the pH range of 7.5 to 8.5, curcumin changes color to red. The anionic form of curcumin, being more water-soluble than the neutral form, exhibits altered chemical reactivity and solubility as the pH becomes more basic.\[21\] In alkaline pH (>pH 10), fully deprotonated (red) curcumin’s molar extinction coefficient is 53,000 dm$^3$ mol$^{-1}$ cm$^{-1}$, with the absorption peak at 467 nm. Debates surround the acidity of the enolic OH versus the phenolic OH among the three proton sites. While calculations favor the enolic OH as the most acidic, differentiating between the two protons based on pH-dependent spectrum shifts can be challenging. Borsari et al. propose a pKa of 12.5 for the enolic proton’s deprotonation and a distinct pKa of 13.6 for the phenolic protons based on 1H-NMR studies. However, these enolic proton values diverge from findings using other techniques.\[22\] The resolution of these pKa discrepancies may be achievable in the future due to the availability of diverse spectroscopic methods.

![Figure 1.3 keto-enol tautomerism, prototropic equilibria, and curcumin degradation products.\[23\]](image_url)

Various types of compounds, such as surfactants, lipids, albumins, cyclodextrins, and biopolymers, into the context of the synthesis or utilization of curcumin. One can create aqueous curcumin solutions. The ideal method for making water-based curcumin solutions with a high concentration is to use micellar solutions including surfactants. However, as aqueous surfactant solutions might interfere with biological investigations, caution must be exercised when utilizing them in biological systems and suitable control tests must be conducted.\[24\]

### 1.5 Curcumin Reactivity:

...
Curcumin features three vital reactive functional groups: a single diketone moiety and two phenolic groups. The biological activity of curcumin is closely tied to several significant chemical processes, including hydrogen donation reactions, both reversible and irreversible nucleophilic addition reactions (Michael reactions), hydrolysis, degradation, and enzymatic reactions. Each of these processes contributes to curcumin’s diverse biological functions, making them of paramount importance.[25]

1.5.1 Reaction with ROS: It has been discovered that curcumin is an effective ROS scavenger, giving it antioxidant action in healthy cells. Reactive Oxygen Species (ROS) is a collective term encompassing various reactive molecules that include both molecular oxidants and free radical oxidants. These ROS play essential roles in various cellular processes and can impact biological systems positively or negatively, depending on their levels and interactions.[26] Curcumin’s three active sites can all be subjected to oxidation through electron transfer and hydrogen abstraction. Numerous research efforts conducted by multiple scientific teams have provided substantial evidence indicating that the phenolic hydroxyl (phenol–OH) group within curcumin is the site from which hydrogen can be most readily abstracted during free radical reactions. This abstraction process leads to the formation of phenoxy radicals, which are stabilized through resonance across the keto-enol structure of curcumin. This resonance stabilization contributes to the stability and behavior of the resulting radicals.[27]

Using curcumin as an illustrative example, peroxyl radicals have the propensity to interact with curcumin, resulting in the formation of curcumin phenoxy radicals. These phenoxy radicals exhibit lower reactivity compared to peroxyl radicals and serve as a defense mechanism against oxidative stress.
stress instigated by Reactive Oxygen Species (ROS). In a fascinating chain of reactions, curcumin takes on chain-breaking antioxidant characteristics similar to those of vitamin E. Curcumin's scavenging responses against a number of different free radicals, including hydroxyl, superoxide, and alkoxy radicals, have been documented in the literature. Curcumin has exhibited a remarkable ability to engage with superoxide radicals, akin to the effectiveness demonstrated by widely recognized lipid-soluble antioxidants. This interaction yields a significant outcome: the catalytic degradation of superoxide radicals, where curcumin acts as a mimic of the enzyme superoxide dismutase (SOD). This unique role enables curcumin to participate in the neutralization of superoxide radicals, thereby mitigating their potentially harmful effects. There aren't many reports in the literature about curcumin's direct reactivity with peroxynitrite. Curcumin is a potent antioxidant against peroxynitrite-induced oxidative stress, according to the stated rate constants and inhibitory doses to stop nitrotyrosine production.

1.5.2 Chemical Degradation and Metabolism: The prevalent molecular oxidant reactions often involve hydrogen peroxide (H2O2) and peroxynitrite (ONOO•). Curcumin's ability to shield cells from oxidative stress induced by an overabundance of these molecular oxidants has been well-documented across a range of biological models. However, you are correct that the existing body of research is somewhat limited when it comes to providing comprehensive explanations of the potential chemical reactions that occur and listing the specific products generated during these processes. There aren’t many reports in the literature about curcumin's direct reactivity with peroxynitrite. Curcumin is a potent antioxidant against peroxynitrite-induced oxidative stress, according to the stated rate constants and inhibitory doses to stop nitrotyrosine production. Thus, the ability to create stable curcumin solutions in culture media has been proven to be of significant benefit. 10% Foetal Bovine Serum (FBS), as well as human blood, are both present. When curcumin is exposed to sunshine, it degrades substantially more quickly. According to some reports, curcumin produces singlet oxygen and other ROS upon photoexcitation. It is truly in charge of curcumin's photobiological and photodynamic action. According to photophysical studies, the lifespan of curcumin's triplet excited state is measured in microseconds, which suggests that the degradation process of curcumin has the potential to progress rapidly and may compete with the generation of singlet oxygen. Photodegradation, which involves the breakdown of curcumin when exposed to light, can occur at a significant rate. Interestingly, the presence of TiO2 nanoparticles has been found to enhance this photodegradation process. This phenomenon can be harnessed for practical applications, such as the removal of turmeric stains from cotton garments. In rats and people, the metabolism of curcumin results in several by-products. Curcumin metabolism can be divided into two main processes: O-conjugation and reduction. Certainly, curcumin can undergo various metabolic transformations, leading to the formation of different products. Here's a breakdown of some of the products you mentioned: O-Conjugation Products: Curcumin Glucuronide: Curcumin can undergo glucuronidation, a
process where a glucuronic acid molecule is attached to it, resulting in curcumin glucuronide. This modification enhances its water solubility and facilitates its excretion from the body. Curcumin Sulphate: Another type of O-conjugation involves the attachment of a sulfate group to curcumin, yielding curcumin sulphate.[33]

**Reduction Products:**
- Tetrahydrocurcumin: Reduction of curcumin's double bonds results in tetrahydrocurcumin, which has hydrogen atoms added to its structure.
- Hexahydrocurcumin: Further hydrogenation produces hexahydro curcumin, a derivative with even more hydrogen atoms added.
- Octahydrocurcumin: The most reduced form is octahydrocurcumin, formed by additional hydrogenation.

**Minor Products:**
- Tetrahydrocurcumin Glucuronide: After reduction, tetrahydrocurcumin can also undergo glucuronidation, leading to the formation of tetrahydrocurcumin glucuronide.
- Dihydrocurcumin Glucuronide: Similar to tetrahydrocurcumin, dihydrocurcumin (resulting from reduction) can also be glucuronidated to produce dihydrocurcumin glucuronide.

**Ferulic Acid:** In some cases, curcumin can be converted into ferulic acid through demethylation, leading to the loss of a methoxy group.

**Dihydroferulic Acid:** Similarly, the reduced form of ferulic acid, known as dihydroferulic acid, can be formed. These metabolic transformations highlight the versatile ways curcumin can be modified in the body. These modifications can influence its bioavailability, metabolism, and biological effects.[34]

1.5.3 **Nucleophilic Addition Reaction of Curcumin:** curcumin’s α,β-unsaturated β-diketo moiety actively participates in nucleophilic addition processes. In these reactions, the unsaturated ketone serves as the electron acceptor, while anions such as -OH (hydroxide), -SH (thiol), and -SeH (selenol) function as electron donors. This specific type of nucleophilic addition is often referred to as the Michael addition. During the Michael addition, the nucleophiles (-OH, -SH, -SeH) add to the unsaturated ketone at the β-carbon, forming a new carbon-carbon bond.[35] This results in a 1,4-addition pattern, producing products that are typically irreversible. However, it’s worth noting that under certain oxidizing and basic conditions, reversibility can be achieved. According to reports, this reaction is incredibly helpful in explaining the biological chemistry of curcumin in live cells. Particularly intriguing has been how biological thiols with -SH groups, such as glutathione, react. Indeed, multiple techniques have allowed for the isolation of curcumin-glutathione conjugates.[36] The production of this additional product would cause cells’ levels of intracellular glutathione to drop, decreasing the body's total antioxidant defence. Although a few publications imply that this is a reversible reaction, it has not yet been established whether or not this reaction is reversible in living cells. In oxidizing environments and at basic pH levels, the reaction involving curcumin's α,β-unsaturated β-diketo moiety and nucleophilic donors like -OH, -SH, and -SeH can become reversible. An essential enzyme in cellular redox equilibrium is thioredoxin reductase. Selenocysteine serves as the enzyme’s active core.
With curcumin, the selenol of selenocysteine easily undergoes 1,4-addition because it is a greater nucleophile at physiological pH. This results in covalently linked species.[37] The efficient suppression of the thioredoxin reductase enzyme by curcumin is thought to be mostly due to this process. Curcumin’s structure and the results of its Michael addition reaction with protein thiols and selenols.

![Chemical structure of curcumin and reaction with protein](image)

**Figure 1.5** Protein thiols and selenols are results of the Michael addition of curcumin where $X = S$ or Se.[38]

while curcumin can participate as a nucleophile in Michael addition reactions with stronger electrophiles, the significance of the methylenic hydrogen in the diketo/enol moiety of curcumin may not hold a prominent role within biological systems. In the realm of chemical modifications, various condensation and addition reactions have been employed to generate chemically modified curcumin derivatives. For instance, semicarbazone and oxime derivatives of curcumin have been synthesized through these reactions. These chemically modified derivatives exhibit enhanced stability and have been subject to investigation for their anti-cancer potential. Remarkably, many studies suggest that these derivatives exhibit greater cytotoxicity towards cancer cells compared to the free form of curcumin.[39]

### 1.6 Phytochemicals liable to Anti-Cancer activity– A Review

#### 1.6.1 Flavonoids:

Despite the enormous advances in our understanding and treatment of cancer, there is still no surefire cure for a wide variety of tumours. Therefore, the fight against malignant growth has recently received a lot of attention from both disease patients and, astonishingly, from doctors as well. Plant-inferred optional metabolites known as phytoestrogens are often divided into three main classes: flavonoids, cumestans, and lignans. Almost all plant families include flavonoids. Flavonoids are among the most well-known rivals in the fight against cancer around the world and are present in a variety of plant parts, including the leaves, stems, roots, blooms, and seeds. Flavonoid subordinates offer a variety of beneficial natural properties, including antibacterial, antiviral, sedative, anticancer, and antagonistic to adversely susceptible actions. Some of these benefits are attributed to flavonoids’ potent anticancer effects, which include metal chelation and antiradical activity (Amin et al., 2007).[40]

The most abundant active components in all plant species are flavonoids. Numerous varieties of plant-derived flavonoids are frequently consumed or used for therapeutic purposes in the human diet. The
inhibition of specific biological catalysts, such as hydrolases, oxidoreductases, DNA polymerases, lipoygenases, and glutathione S-transferases, is attributed to flavonoids. A few stomach-related substances, such as -amylase, trypsin, and lipase, are also blocked by them (Koshihara et al., 1984; Griffiths, 1986; Reddy et al., 1994; Sadik et al., 2003). Hus, an increasing number of licensed physicians are advocating pure flavonoids to cure a wide range of important basic ailments.\textsuperscript{[41]}

Figure 1.6 Curcumin degradation products as outlined by Wang et al.
1.7 Anti-cancer Activity: Inhibition of Carcinogenesis

Curcumin has been investigated for its impact on various human carcinomas, such as melanoma, head and neck, breast, colon, pancreatic, prostate, and ovarian cancers. Epidemiological studies explain India’s low prevalence of colon cancer by the curcumin-rich foods’ chemo preventive and antioxidant effects. Curcumin’s anti-cancer properties are multifaceted, targeting multiple levels of regulation in cellular development and apoptosis processes.\(^{[43]}\) It operates across various stages of carcinogenesis, spanning from the initial events triggering DNA mutations to tumorigenesis, growth, and metastasis. Apart from its vertical impact on transcription factors, oncogenes, and signaling proteins, curcumin also exerts influence across these different temporal stages of carcinogenesis. With its diverse array of actions and impacts on cellular development control mechanisms, curcumin stands as a promising contender for potential use as a chemotherapeutic agent against a wide range of human malignancies.\(^{[44]}\)\(^{[45]}\)

**Figure 1.8 An overview of the anti-cancer effects of curcumin**

Curcumin’s impact on cancer-related processes is extensive and involves multiple mechanisms: NF-κB Pathway Suppression: Curcumin targets the NF-κB pathway, reducing the expression of NF-κB-regulated genes like TNF, COX-2, cyclin D1, c-myc, MMP-9, and interleukins. This inhibits key factors involved in carcinogenesis. IKB Activity Inhibition: Curcumin obstructs IKB (inhibitor of NF-κB) activity, disrupting the NF-κB signaling cascade and subsequently hindering the expression of pro-cancer genes.\(^{[46]}\) Cell Cycle and Apoptosis Control: Curcumin’s effects on p16 and p53 overexpression contribute to controlling the cell cycle and promoting apoptosis, preventing uncontrolled cell growth. Angiogenesis and Metastasis Inhibition: Curcumin modulates autophagy and suppresses various
growth factors, including VEGF, COX-2, MMPs, and ICAMs. This dual action impedes tumor angiogenesis (formation of new blood vessels) and metastasis (cancer spread).[47] Overall Anti-Inflammatory and Anti-Growth Effects: By targeting multiple factors and pathways, curcumin creates an environment that discourages cancer development, growth, and spread. It’s important to recognize that while these actions have been observed in various studies, the translation of curcumin’s effects from the lab to clinical applications involves complexities and challenges. Clinical trials are essential to determine its efficacy and safety in treating cancer in humans displays inhibitory effects during the early stages of carcinogenesis. Curcumin has been demonstrated to have the capacity to inhibit DNA mutagenesis brought on by UV radiation and to promote cellular SOS functions. Curcumin also affects the Phase I and Phase II enzymes within the hepatic cytochrome P450 enzyme system, which play roles in oxidizing and detoxifying harmful substances. These effects are in addition to curcumin’s capability to inhibit nitric oxide (NO) production and its scavenging ability for DNA-damaging superoxide radicals. Phase I enzymes, including cytochrome P450 isoforms and p450 reductase, which become active in response to toxin exposure and generate various carcinogenic metabolites during the oxidation of such substances, have been discovered to be inhibited by curcumin during the early stages of carcinogenesis. Curcumin activates Phase II enzymes (such as glutathione S-transferase, glutathione peroxidase, and glutathione reductase) that play a role in the detoxification of hazardous compounds. In numerous animal models representing diverse tumor types, including oral cancer, mammary carcinoma, and intestinal tumors, curcumin's inhibitory effects on carcinogenesis have been demonstrated.[48]

1.8 Curcumin’s effects on cancer:
Multiple studies have substantiated that curcumin exerts potent anti-cancer effects by restraining the development of new blood vessels from existing ones, a process known as angiogenesis. Angiogenesis involves a number of processes, including endothelial cell activation, proliferation, invasion, and migration. Multiple inhibition of these stages by curcumin has been demonstrated to inhibit angiogenesis in many malignancies. Additionally, research revealed that curcumin suppressed VEGF Receptor signaling in vivo to prevent lymph Angiogenesis encompasses the growth of new lymphatic vessels, a pivotal process that holds a significant role in the metastatic spread of cancer. Many fried foods are used in Indian diets, which may also contribute to gastrointestinal tract malignancies as a result of the cooking process, which produces heterocyclic amines (HA) that are potentially carcinogenic or mutagenic. According to certain animal research, giving mice traditional Indian foods like deep-fried veggies caused a 20% increase in stomach cancer.[49] Contrary to other nations, India’s stomach tumour incidence rates are considered to be moderate to low. Since stomach tumours are frequently caused by the cancer-causing bacterium Helicobacter pylori, The substantial utilization of natural substances like turmeric might contribute to elucidating their protective effects against cancer. Anticancer mechanism of bioavailable curcumin along with a few examples of tumours that curcumin or curcumin composites increased.
1.8.1 Colon Cancer

The challenge of achieving effective dosages of phytochemicals through oral administration, particularly from dietary sources, is a notable issue in harnessing the anti-cancer benefits of these bioactive compounds found in foods and plants. In a study by Aromokeye and Si, the combination of two phytochemicals, curcumin and luteolin, both present in food, demonstrated a stronger inhibitory effect on colon cancer growth.\(^{[50]}\) The research delved into potential molecular mechanisms underlying this anti-colon cancer action. The combined treatment of curcumin (Cur) at 15 M and luteolin (LUT) at 30 M (C15L30) effectively suppressed the proliferation of human colon cancer CL-188 cells. This synergistic effect was also observed in additional colon cancer DLD-1 cells, showcasing the potency of C15L30 across various colon cancer cell types. The combined treatment showed a synergistic reduction in wound healing in CL-188 cells. In mice harboring xenografts of CL-188 cell-derived tumors, the synergistic impact continued as the combination of Cur and LUT (administered at 20 mg/kg/day and 10 mg/kg/day, respectively, through IP injection for 5 days over 2 weeks) significantly reduced tumor growth. Western blot analysis revealed that the combination of Cur and LUT led to a synergistic decrease in Notch1 and TGF-β protein levels, both in CL-188 cells and xenograft tumors. Interestingly, individual treatments with Cur and LUT had limited effects on tumor necrosis. However, the combined Cur and LUT treatment resulted in a synergistic promotion of necrosis, as confirmed through tumor pathological investigation. These findings highlight the potential synergy between curcumin and luteolin in inhibiting colon cancer growth and suggest their combined use as a promising approach for combating this type of cancer.\(^{[51]}\)

1.8.2 Lung Cancer

Conventional chemotherapy drugs have certain limitations when employed for lung cancer treatment, such as adverse side effects, inconsistent drug release, poor absorption, and the emergence of drug resistance. To overcome these issues, a new approach involving modified nanoparticles named T7-CMCS-BAPE (CBT) was developed. These nanoparticles, created using carboxymethyl chitosan (CMCS),...
aimed to mitigate the shortcomings of free drugs and improve therapeutic outcomes. CMCS allowed precise control of drug release based on pH and ROS levels, and it could also target the transferrin receptor (TfR) found on lung cancer cells. The study revealed that docetaxel (DTX) and curcumin were loaded into the nanoparticles with drug-loading contents of 7.82% and 6.48%, respectively. These nanoparticles maintained good biosafety even at high concentrations of 500 g/mL. Remarkably, in comparison to other nanocarriers carrying DTX and curcumin separately, as well as DTX alone, the T7-CMCS-BAPE-DTX/CUR (CBT-DC) complexes exhibited superior in vitro and in vivo anti-tumor effects. Furthermore, CBT-DC improved the immune-suppressed microenvironment, aiding in inhibiting tumor growth.\textsuperscript{52}[53][54]

1.8.3 Prostate Cancer

Prostate cancer stands as the most prevalent tumor in the United States. Its propensity to advance into a hormone-resistant stage contributes to its aggressive nature. Effectively halting tumor growth and preventing the dissemination of metastatic disease poses a significant challenge in the clinical management of prostate cancer (PC). Recent years have witnessed concerted efforts to discover novel compounds for PC therapy, yielding promising advancements in this domain. Many drugs utilized in PC therapy lead to resistance, leading to the emergence of metastatic castration-resistant forms (mCRPC), which renders the cancer almost incurable. Among those grappling with mCRPC, the readily available dietary supplement curcumin emerges as an appealing therapeutic avenue. The results revealed that curcumin administration, akin to chemotherapy drugs like paclitaxel, cisplatin, and docetaxel, exhibited dose-dependent reductions in the viability of DU145 and PC-3 cells. The study also delved into the impact of EGFR-mediated signaling on ERK activation within DU145 and PC-3 cells. The findings indicated elevated EGFR expression in these cell lines, with both curcumin and chemotherapy drugs leading to lowered EGFR levels and diminished ERK activation. Ultimately, both curcumin and chemotherapy agents demonstrated the capacity to induce apoptosis and shrink the size of DU145 and PC-3 spheroids, both in regular conditions and Matrigel environments.\textsuperscript{55}[56]

1.8.4 Pancreatic Cancer

The increasing resistance of pancreatic cancer to chemotherapy has become a formidable challenge in the realm of clinical practice. Pancreatic carcinoma stands as a malignancy with a notably high mortality rate, necessitating the development of a potent therapeutic approach. Sestrins, a cluster of stress-associated proteins, wield influence over metabolism and cell growth by serving as antioxidants. Turmeric, rich in curcumin, a natural pigment, exhibits a range of pharmacological actions including anti-inflammatory, antioxidant, and potential anticancer properties, as supported by various studies. The specific mechanism and potential synergy between curcumin and the sestrin family in inhibiting tumor growth have yet to be fully explored.\textsuperscript{57} An investigation sought to uncover the molecular processes potentially responsible for the combined anticancer effects of curcumin and
sestrin family members on pancreatic malignancy. The findings demonstrated that sestrin2 and curcumin collaboratively produced a profound reduction in pancreatic cancer. Notably, through precise targeting of the Nrf2/Keap1/HO-1/NQO-1 pathway, sestrin2, in tandem with curcumin, exhibited a suppressive effect on pancreatic cancer. The strategic targeting of sestrin2 by curcumin could hold promise as a valuable therapeutic strategy for combating pancreatic cancer. In a separate study, a robust solid-phase method was proposed for the combined synthesis of a compact library of curcumin analogs, resulting in high yields and purity. Previously ineffectual outcomes in pancreatic cancer cells were transformed into substantial growth inhibition and effective cell death in PC3 prostate cancer cells.[58]

1.8.5 Breast Cancer:

Breast cancer, the leading cause of mortality among women, presents a significant challenge. Despite treatments like lumpectomy, radiation therapy, chemotherapy, and endocrine therapy, a meta-analysis of 21 retrospective studies has shown that breast cancer recurrence rates remain high. This underscores the persistent need for novel and effective therapeutic strategies. In a study involving MCF10A human mammary epithelial cells and MCF7 breast cancer cells, curcumin treatment exhibited a concentration-dependent reduction in telomerase activity. This outcome correlated with the downregulation of hTERT by curcumin, though not through the c-Myc mRNA pathway. Another examination involving MDA-MB-231 and BT-483 breast cancer cell lines investigated curcumin's impact on NF-B, matrix metalloproteinases (MMPs), and cell-cycle regulatory proteins. This study confirmed previous findings across different breast cancer cell lines by validating curcumin's ability to inhibit NF-B, resulting in an antiproliferative effect. Moreover, cyclic D1 in MDA-MB-231 cells and CDK4 in BT-483 were reduced following curcumin treatment. In the MDA-MB-231 cell line, the combination of arabinogalactan and curcumin intensified apoptosis induction by elevating ROS levels, disrupting the mitochondrial membrane, and reducing glutathione. Curcumin's influence on breast tumor growth was multifaceted.[59] It upregulated the p53 gene and lowered the levels of the ki-67 antigen, leading to the inhibition of breast tumor growth. Another study on MDA-MB-231 cells highlighted curcumin's inhibition of inflammatory cytokines CXCL1/2. Additionally, curcumin impeded the expression of genes that promote metastasis, including the chemotactic receptor CXCR4, by blocking CXCL1 and CXCL2. Furthermore, dimethyl curcumin (ASC-J9) demonstrated effectiveness against estrogen-dependent breast cancer by inhibiting various steroid receptor types. This contributes to the expanding understanding of curcumin's potential in breast cancer treatment.[60]

1.9 Pharmacological Effects of Curcumin:

1.9.1 Antimicrobial and Antiviral Effects: Penicillium notatum, and Aspergillus niger, nanocurcumin (discussed above) demonstrated significantly higher aqueous dispersion than curcumin. According to
transmission electron microscope research, Nanocurcumin particles exhibited effective disruption of bacterial cell walls, resulting in a bactericidal effect. The antibacterial action of nanocurcumin was particularly potent. In a study involving mice with Helicobacter pylori infection, curcumin demonstrated antibacterial properties by suppressing the production of matrix metalloproteinase-3 (MMP-3) and MMP-9. Furthermore, when tested against 14 different Candida strains, curcumin displayed antifungal activity. Specifically, it notably reduced ergosterol content in the fungal cell membrane, proteinase secretion from fungal cells, and H+ extrusion from Candida albicans and Candida glabrata. However, these effects were not as pronounced as those observed with the antifungal drug fluconazole (azole).[61]

Curcumin exhibited inhibition of HIV-1 replication pathways by preventing Tat-induced long terminal region (LTR) transactivation. It achieved this by specifically halting Tat-mediated downregulation of HDAC1 expression, inhibiting Tat-mediated dissociation of HDAC1 from LTR, and blocking Tat-mediated binding of p65/NF-B to LTR promoters.[62]

1.9.2 Inflammation and Immunity: Recent investigations have provided strong support for the well-established claims that curcumin possesses potent immunomodulatory and anti-inflammatory properties. Under physiological sheer stress conditions, curcumin-treated HIMEC (human intestinal microvascular endothelial cells) exhibited reduced leukocyte adhesion to TNF-α/LPS-activated HIMEC monolayers. Additionally, curcumin suppressed the expression of vascular cell adhesion molecule-1 (VCAM-1) induced by TNF-α/LPS. In human umbilical vein endothelial cells stimulated by TNF, curcumin effectively hindered the transcriptional and translational expression of intracellular cell adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), and interleukin-8 (IL-8), leading to decreased monocyte adhesion. In an Indian study, dietary curcumin offered protection against endotoxin shock in mice by impeding neutrophil transmigration and infiltration into the liver after LPS injections. This effect was associated with a substantial reduction in ICAM-1 and VCAM-1 expression in the liver and lungs.[63]

1.9.3 Cardiovascular System: The potential pharmacological effects of curcumin on the cardiovascular system, particularly its protective attributes, have gained significant attention in recent times. A Romanian study revealed that curcumin possesses the ability to counteract the pro-inflammatory effects of the cytokine resistin in human endothelial cells. Curcumin exhibited several positive outcomes, including inhibiting the expression of P-selectin and fractalkine, reducing the activation of nicotinamide adenine dinucleotide phosphate (NADPH), decreasing monocyte adherence to human endothelial cells, and preventing an increase in intracellular ROS (reactive oxygen species) levels.[64]

1.9.4 Cancer: The potential pharmacological effects of curcumin are indeed vast and diverse, spanning
various aspects of health and disease. Here’s a summary of the key points from your text:

1.9.4.1 **Cardiovascular Effects:** Curcumin exhibits anti-inflammatory effects by countering pro-inflammatory cytokines. It reduces vascular superoxide generation, oxidative stress, and increases glutathione levels. Curcumin reduces atherosclerosis by affecting lipid profiles, cholesterol metabolism, and inhibiting atherogenic processes. It has anti-angiogenic properties, reducing microvessel density and plasma VEGF levels.

1.9.4.2 **Anticancer Properties:** Curcumin has garnered substantial interest as a potential cancer chemo preventive and chemotherapeutic agent. It inhibits angiogenesis and metastasis in various cancer models. Curcumin influences various cellular signaling pathways and gene expression, promoting apoptosis and inhibiting proliferation. It has shown promise against several cancer types, including breast, cervical, oral, prostate, and more.

1.9.4.3 **Neurological and Neuroprotective Effects:** Curcumin has shown potential in neuroprotection and neurotherapeutics. It activates the Wnt/-catenin signaling pathway, which could have implications for Alzheimer’s disease. Curcumin may directly interact with amyloid-(A) oligomers and fibrils. It exhibits antidepressant and anti-epileptic properties and supports neuroprotection.[65][66]

1.9.4.4 **Diabetes and Obesity Management:** Curcumin has shown anti-diabetic effects by improving insulin sensitivity, modulating antioxidant enzymes, and reducing inflammatory markers. It affects glucose metabolism, lipid profiles, and insulin signaling. Curcumin reduces diabetic complications like diabetic retinopathy and has anti-lipolytic effects.

1.9.4.5 **Miscellaneous Effects:** Curcumin demonstrates anti-inflammatory and immunomodulatory properties. It has been studied for its effects on endothelial function, including anti-thrombotic and vasodilatory effects. Curcumin has been explored for its effects on lipid metabolism, fatty acid synthesis, and adipogenesis.

1.9.4.6 **Limitations and Challenges:** Despite its potential, curcumin’s low bioavailability, stability, and poor solubility can limit its therapeutic applications. Researchers are exploring various strategies to enhance curcumin’s delivery and bioavailability. It’s important to note that while these studies suggest potential therapeutic benefits of curcumin, the translation of these findings to clinical practice often requires further research, including human trials. Curcumin’s multifaceted pharmacological effects make it an intriguing compound with diverse potential applications in health and disease management.[67]

1.9.5 **The Renal System:** The recent studies you’ve mentioned highlight the potential protective effects of curcumin in the context of renal health and disease. Here’s a summary of the key findings:

1.9.5.1 **Acute Renal Injury:** Curcumin pretreatment demonstrated protective effects in rats that underwent acute renal injury due to ischemia and reperfusion. Curcumin reduced plasma levels of various pro-inflammatory cytokines, including TNF-, IL-1, IL-12, IL-18, and IFN-. It also decreased apoptosis in renal and pulmonary tissues by blocking TGF-β and caspase-3 production.
1.9.5.2 Autosomal Dominant Polycystic Kidney Disease (ADPKD): Curcumin showed potential as a treatment for ADPKD, a genetic disorder characterized by the growth of numerous cysts in the kidneys. In mice with a gene loss linked to ADPKD, curcumin treatment improved renal histology, reduced cystic and kidney weight/body weight ratios, and decreased the proliferation index. The effects were attributed to curcumin's inhibition of the mTOR and STAT3 pathways.

1.9.5.3 Chronic Kidney Disease (CKD): Curcumin had an impact on peripheral blood mononuclear cells isolated from individuals with chronic kidney disease. It significantly reduced the production of pro-inflammatory cytokines IL-6 and IL-1 by these cells. These findings suggest that curcumin holds potential in mitigating the inflammatory processes and cellular responses associated with kidney injuries and diseases. As with many areas of research, further studies, especially clinical trials, will be needed to fully understand the efficacy and safety of curcumin as a therapeutic intervention in these kidney-related conditions.[68][69][70]

1.9.6 The Respiratory System:
The studies you've mentioned highlight the potential protective effects of curcumin in the context of lung health, particularly after cardiopulmonary bypass (CPB) and in the treatment of certain lung-related conditions. Here's a summary of the key findings:

1.9.6.1 Cardiopulmonary Bypass (CPB): In an in vivo study with rats, curcumin pretreatment had a significant protective impact on the lungs following cardiopulmonary bypass (CPB). Curcumin reduced CPB-induced concentrations of pro-inflammatory cytokines IL-8 and TNF- as well as MMP-9 in lung tissue, bronchoalveolar lavage fluid, and plasma. The lung injury score was decreased in rats treated with curcumin, and the expression of genes related to inflammation and immune response (NF-B, toll-like receptor 4, myeloid differentiation main response gene 88) was downregulated in lung tissue.

1.9.6.2 Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Dysfunction: In vitro studies focused on cystic fibrosis, specifically on the CFTR protein with the G551D mutation. Curcumin, in combination with genistein, showed potential in improving CFTR function. When combined with maximum doses of genistein, curcumin allowed the G551D mutant CFTR to achieve up to 50% of the function of the wild-type CFTR. Curcumin and genistein used in combination at lower concentrations were also effective in treating the gating dysfunction of G551D-CFTR. These findings suggest that curcumin may have beneficial effects on lung health, including mitigating inflammation and improving lung function in certain conditions. As always, further research, including clinical trials, will be necessary to fully understand the potential therapeutic applications of curcumin in these contexts.[71]

1.9.7 Other Body system: In a recent study, a potential mechanism for curcumin's effectiveness in the treatment of gastrointestinal conditions such diarrhea, stomach cramps, and irritable bowel syndrome was revealed. One dose of curcumin given intragastrically to rats resulted in a considerable reduction in the amount of barium sulphate that was the studies you've mentioned highlight the effects of
curcumin on various physiological systems, including the gastrointestinal, integumentary, and reproductive systems. Here’s a summary of the key findings:

1.9.7.1 Gastrointestinal System: Curcumin was found to suppress intestinal motility in the small intestine, suggesting its potential to affect gut function and transit.

1.9.7.2 Integumentary System (Skin and Wound Healing): In wound healing processes, curcumin exhibited a biphasic effect. Low dosages (1–5 μM) promoted wound healing, while high doses inhibited it. Curcumin’s effect on wound healing was mediated through the activation of stress response pathways like Nrf2 and heme oxygenase-1 (HO-1), acting as a hormetin. Hormetins are compounds that induce hormesis, a process in which low doses of a stressor can enhance resilience and health.[72][73]

1.9.7.3 Reproductive System: Curcumin exhibited dose-dependent effects on the reproductive system. It inhibited the forward motility of murine and human sperm, the capacitation/acrosome reaction, and murine in vitro fertilization. Intravaginal administration of curcumin in mice led to a significant decrease in fertility. In a rat model of endometriosis, curcumin displayed anti-angiogenic effects. It reduced the number of heterotopic endometrial microvessels and the production of vascular endothelial growth factor (VEGF), suggesting a potential role in managing conditions related to abnormal angiogenesis. These findings underscore the complex and multifaceted effects of curcumin on different physiological systems. While the studies provide insights into its potential therapeutic applications, further research is needed to fully understand the mechanisms underlying these effects and to determine the optimal dosages for specific applications.[74]

1.10 Metabolism and Bioavailability of Curcumin: Absolutely, you’ve provided accurate information about curcumin, the main active compound found in turmeric. Curcumin’s chemical structure, insolubility in water, solubility in organic solvents, and stability in acidic environments are key characteristics that contribute to its bioavailability and potential therapeutic applications. Its unique properties have made it a focus of extensive research and exploration for various health benefits. Chemically speaking, molecule is symmetric, has two aromatic rings that are identical to one another, and has conjugate double bonds that are used as efficient electron donors to prevent the generation of ROS. Indeed, you’re correct.[75] Curcumin’s presence in turmeric, a common spice used in many Asian cuisines, has led to its widespread use in food preparations. The vibrant yellow color of turmeric is attributed to curcumin, making it a popular natural coloring agent. The growing interest in curcumin’s pharmacological properties, such as its antioxidant, anti-inflammatory, anti-cancer, and neuroprotective effects, has extended its relevance beyond culinary applications. Researchers and scientists have been investigating its potential health benefits, which has led to an increased global awareness of curcumin and its potential therapeutic uses. As a result, curcumin supplements and extracts are now available for those seeking to harness its potential health benefits more directly, especially those that are anti-inflammatory and antioxidant. It’s great to hear that recent research through a meta-analysis has highlighted curcumin’s potential as a free radical scavenger and an
inhibitor of malondialdehyde synthesis. This indicates that curcumin could be effective in increasing antioxidant levels and combating oxidative stress, especially in individuals who are more susceptible to such stress due to certain health conditions. Curcumin’s antioxidant properties have been a subject of interest in various studies, and this finding adds to the growing body of evidence suggesting its potential health benefits. Antioxidants play a crucial role in protecting cells and tissues from damage caused by oxidative stress, which is linked to various chronic diseases and the aging process. The dosage and length of the treatment were factors in the decrease of oxidative stress caused by curcumin administration. A comprehensive overview of curcumin’s potential benefits and challenges related to its bioavailability and metabolism. Indeed, curcumin holds promise for the treatment of various human illnesses, and its safety has been recognized by regulatory bodies such as the US Food and Drug Administration (FDA) and JECFA. However, its limited bioavailability due to poor absorption, rapid metabolism, and excretion rate presents a challenge for its effective therapeutic use.[76] Curcumin’s metabolism involves both phase I and phase II reactions, which lead to the formation of various metabolites, including glucuronide and sulfate conjugates. These conjugated metabolites are typically detected in body fluids, organs, and cells, indicating that curcumin is subjected to extensive metabolism before being excreted. While curcumin’s metabolites are readily detected, the concentration of intact curcumin in blood plasma and urine is generally very low after oral administration. This limitation can impact its effectiveness as a therapeutic agent, as higher levels of curcumin are often required to achieve the desired pharmacological effects. Researchers have explored different strategies to improve curcumin’s bioavailability, such as using formulations that enhance its solubility and stability. For example, combining curcumin with certain compounds or encapsulating it in nanoparticles has been shown to increase its absorption and extend its presence in the bloodstream.[77] It’s important to continue studying curcumin’s pharmacokinetics and exploring ways to enhance its bioavailability to fully harness its potential health benefits. As research in this area advances, we may discover more effective ways to deliver curcumin for therapeutic purposes.
Figure 1.10 depicting the metabolism of curcumin and its reduction pathway, as well as the two conjugation pathways: glucuronidation and sulfatation.

The limited bioavailability of curcumin following oral treatment may significantly limit its pharmacological activity and, as a result, its clinical use. As a result, many delivery systems have been created to boost the bioavailability of curcumin, including micelles, liposomes, phospholipid complexes, macroemulsions, nanostructured lipid carriers, and biopolymer nanoparticles.\(^{[78]}\)

In particular, Kato et al. used a novel formulation of curcumin that was dispersed with colloidal nanoparticles to improve hyperglycemia by stimulating the release of GLP-1 (glucagon-like peptide 1) and the subsequent insulin secretion, suggesting a potential use of curcumin formulation in the treatment of diabetes. Even though the dosage is crucial since it needs to be kept very low to prevent toxicity, such formulations might also be useful against osteoarthritis and inflammatory state. Recently, Chen et al. convincingly showed that supplementing mice with nanobubble curcumin extract improved their health and exercise performance while also assisting the mice in overcoming physical exhaustion. Additionally, its interaction with the gut and the potential role of the gut microbiota in
mediating its effects. The connection between curcumin and the gut microbiota is indeed a fascinating area of study that holds great promise for understanding the mechanisms underlying its biological activities. Piperine, found in black pepper, is known to enhance the bioavailability of curcumin by inhibiting enzymes that break down curcumin in the liver and intestines. This inhibition allows curcumin to remain in the body for longer periods, potentially leading to greater therapeutic effects. This synergistic effect between piperine and curcumin exemplifies the intricate interplay between natural compounds and their ability to enhance each other's properties. The observation that curcumin's bioavailability is enhanced when consumed as fresh or powdered turmeric, as opposed to isolated supplements, suggests that there might be other compounds in turmeric that aid in its absorption or utilization within the body. This phenomenon, often referred to as the "turmeric matrix effect," underscores the complexity of natural compounds and the potential benefits of consuming them in their whole, unprocessed forms. Furthermore, the potential impact of curcumin on the gut microbiota is a particularly exciting avenue of research. The gut microbiota is known to influence various aspects of human health, including metabolism, immune function, and inflammation. Emerging evidence suggests that curcumin could influence the composition and diversity of the gut microbiota, potentially contributing to its broader health effects. Research has shown that curcumin can interact with gut epithelial cells and modulate signaling pathways involved in inflammation and barrier function. It's also suggested that curcumin's presence in the gut could directly affect microbial populations, leading to a cascade of effects that influence overall health. In summary, the interplay between curcumin, gut microbiota, and the gut environment represents a captivating area of exploration. As researchers delve deeper into this field, we are likely to gain a more comprehensive understanding of how curcumin exerts its beneficial effects on various health conditions, potentially opening up new avenues for therapeutic interventions and personalized treatments.

1.11 Extraction of Curcumin from Turmeric and Detection:
A comprehensive overview of the extraction and detection methods used for curcumin, highlighting the various techniques and instruments employed to isolate and quantify this compound from turmeric. This information sheds light on the complexity and sophistication of the processes involved in studying and utilizing curcumin for various purposes. The extraction of curcumin from turmeric is a crucial step in obtaining this bioactive compound for research and commercial applications. Different solvents and extraction techniques are employed to achieve high yields of curcumin while maintaining its purity and minimizing the use of organic solvents, especially in food applications. The use of supercritical carbon dioxide extraction and enzyme pretreatment are examples of innovative approaches to enhance curcumin yield while ensuring environmentally friendly and economically viable processes. The analysis and detection of curcumin are equally important to ensure accurate quantification and quality control. Various methods, such as absorption detectors, liquid chromatography (HPLC and UPLC), mass spectrometry (LC/MS), and capillary electrophoresis, are employed to detect and quantify curcumin in different matrices. The sensitivity of fluorescence
detection, particularly in the 400–450 nm range, makes it a preferred method for detecting low concentrations of curcumin. The integration of chromatographic and spectroscopic techniques allows researchers to effectively separate and detect curcumin, determine its concentrations in various samples, study its pharmacokinetics, metabolism, and distribution, and ensure the quality and authenticity of curcumin-containing products. Overall, the detailed extraction and detection methods you've described showcase the multidisciplinary nature of curcumin research and its applications, as well as the continuous efforts to optimize and refine these techniques for both scientific and industrial purposes.[82]
2. LITERATURE SURVEY

2.1 Bingjing Zeng et al, (2020)[83] conducted a study on the clinical effects of curcumin in augmenting cancer therapy. Curcuma longa, commonly known as turmeric, holds significant importance as a medicinal herb and spice in Asia. The rhizome of Curcuma longa contains curcumin (diferuloylmethane), a hydrophobic bioactive compound. Owing to its diverse range of biological and pharmacological activities, curcumin has gained substantial attention in recent times. Nevertheless, its practical medicinal applications have been hindered by challenges such as low water solubility, inadequate bioavailability, and rapid metabolism.

2.2 Adhimoolam Karthikeyan et al, (2020)[84] conducted a study on the clinical effects of curcumin in augmenting cancer therapy. Curcuma longa, commonly known as turmeric, holds significant importance as a medicinal herb and spice in Asia. The rhizome of Curcuma longa contains curcumin (diferuloylmethane), a hydrophobic bioactive compound. Owing to its diverse range of biological and pharmacological activities, curcumin has gained substantial attention in recent times. Nevertheless, its practical medicinal applications have been hindered by challenges such as low water solubility, inadequate bioavailability, and rapid metabolism. To address these limitations and unlock its therapeutic potential, researchers have been dedicated to enhancing the biological and pharmacological properties of curcumin. One promising approach involves the utilization of effective delivery methods, particularly nanoencapsulation. Through the development of curcumin nanoformulations (Nanocurcumin), researchers have managed to amplify the entirety of curcumin's biological and pharmacological effects, a feat previously not extensively achievable. As per the collective efforts and existing literature, Nanocurcumin exhibits significant potential, thereby overcoming some of the obstacles associated with curcumin's utilization in therapeutic contexts.

2.3 Tomesh M.A. et al, (2019)[85] conducted a study focusing on Curcumin and its Derivatives as Promising Anticancer Agents. A significant global health challenge revolves around cancer, ranking as the second leading cause of death worldwide. Despite substantial advances in cancer therapy, its prevalence and fatality rate remain alarmingly high.
Consequently, the scientific community places immense importance on devising cancer treatments that are both more efficacious and less detrimental. In the past twenty years, curcumin, the bioactive compound found in the Curcuma longa plant, has garnered substantial attention due to its potential roles as an antioxidant, anti-inflammatory agent, and potential anticancer agent. Drawing from existing literature encompassing experimental and clinical assessments of curcumin’s impact on cancer cell lines, the study provides a comprehensive overview of the medicinal chemistry and pharmacology of curcumin and its derivatives, specifically in relation to their anticancer properties. The review includes insights into their primary mechanisms of action and their interactions with cellular targets. Furthermore, the study underscores the latest advancements in drug delivery techniques aimed at efficiently transporting curcumin to cancer cells.

2.4 A. Marchiani et al, (2014) conducted Curcumin, the primary yellow pigment derived from turmeric, a widely utilized spice in Asian cooking and extensively integrated into Ayurvedic herbal treatments, holds significant importance. Multiple research studies have indicated that curcumin could serve as both a preventive and chemotherapeutic agent against colon, skin, oral, and intestinal cancers. Renowned for its anti-inflammatory and antioxidant attributes, curcumin showcases remarkable reactivity with peroxyl radicals, functioning as a potent scavenger of free radicals. Recent experimental investigations have highlighted the potential of curcumin in Alzheimer’s disease prevention and treatment. Notably, studies have shown that when curcumin is peripherally injected into aged Tg mice, it effectively crosses the blood-brain barrier and binds to amyloid plaques, leading to a marked reduction in amyloid levels and plaque formation. This review will provide an overview of the latest advancements in the medicinal chemistry of curcumin and similar compounds with curcumin-like properties.

2.5 Hoehle, S.I. et al, (2011) conducted Curcumin, a yellow polyphenol pigment extracted from the rhizomes of Curcuma longa Linn plant, serves as a natural antioxidant with diverse pharmacological uses and therapeutic qualities. With historical use in traditional medicine and its role as a food preservative and coloring agent, its potential is well-acknowledged. We isolated microorganisms from human feces capable of converting curcumin, with the most active one being identified as Escherichia coli, revealing an
unexpected capability of E. coli in curcumin transformation. The enzyme responsible for curcumin conversion was purified from E. coli and its properties were examined. The native enzyme displayed a molecular weight of approximately 82 kDa and consisted of two identical subunits. It exhibited a specific preference for curcumin, demonstrating a restricted range of substrates. The process of microbial curcumin metabolism by this enzyme involved a two-step reduction: first, curcumin was transformed into an intermediate product, dihydrocurcumin, and then into the end product, tetrahydrocurcumin, with a dependency on NADPH. We named this enzyme "NADPH-dependent curcumin/dihydrocurcumin reductase" (CurA) and identified the corresponding gene (curA). Through a homology search using the BLAST program, we found that this unique enzyme, involved in curcumin metabolism, belongs to the medium-chain dehydrogenase/reductase superfamily.

**2.6 Michael W.A. et al, (2008)**[^88] conducted The natural compound curcumin has been acknowledged for its medicinal qualities and is employed in the treatment of numerous illnesses. However, it remains uncertain whether its effectiveness arises from its versatile structure or from the properties of the α,β-unsaturated 1,3-diketone part at its core. To investigate this matter, derivatives with electron-rich pyrazole and isoxazole structures were synthesized and assessed against two types of breast cancer cells. As a result, several compounds displaying anti-proliferative effects in the low micromolar to mid nanomolar range were discovered. A study involving conjugate addition was also conducted to compare the electrophilic nature of the diketone, pyrazole, and isoxazole derivatives.

**2.7 P.K. Mukherjee et al, (2006)**[^89] conducted a study on the rhizomatous herbaceous perennial Curcuma longa L., which grows to a height of three to five feet and is cultivated extensively in various tropical nations including Asia, India, China, and others. The study revealed that naturally occurring compounds like curcumin, desmethoxycurcumin, and bisdemethoxycurcumin derived from C. longa effectively inhibit the glucosidase enzyme. Among these compounds, bisdemethoxycurcumin demonstrated the highest effectiveness with an IC50 value of 23 M, displaying inhibition at a concentration twice as low as that of acarbose, a known inhibitor. The research explored the potential antibacterial properties of an ethanolic extract from...
Curcuma longa L. rhizomes against antibiotic-resistant bacteria. These rhizomes are known to contain a range of bioactive substances, such as those with anticancer, antidepressant, antibacterial, anti-aging, and antidiabetic properties. Given the escalating issue of antibiotic-resistant bacteria, the study aimed to identify new sources of antibiotics. Specifically, it investigated the antibacterial effects of ethanolic Curcuma longa L. rhizome extract on three bacterial strains: Proteus mirabilis, Acinetobacter baumannii, and Multidrug-Resistant Klebsiella pneumoniae (MDR-K).
3. AIM AND OBJECTIVES

3.1 AIM:
To Formulate and Evaluate Herbal Tablet of Curcumin for Anticancer Activity.

3.2 OBJECTIVES:
1. To formulate tablet of Anticancer Activity using Curcumin.
2. To formulate Curcumin tablet using Wet Granulation Method.
3. To evaluate and characterize the formulation with respect to the various physical parameters.
4. To study the drug release kinetics.
5. To conceal the flavor, odor, or color of the medication.
6. To formulate tablets that remain chemically and physically steady over an extended duration.
7. To develop tablets that exhibit consistent weight and content of the medication.
8. To design tablets that achieve the necessary level of bioavailability as per the indicated requirements.
9. To formulate tablets with a sophisticated product appearance that is devoid of any tablet imperfections.
4. PLAN OF WORK

The intended research endeavor was organized in the following manner:

1. Review of Existing Literature.
3. Plant acquisition and authentication.
4. Making crude drug ready for extraction
5. A physico-chemical assessment Calculating extractive values.
6. Determination of extractive values
7. Extraction of plant material using several solvents in ascending polarity order.
8. Plant extract preliminary phytochemical investigations.
9. The total flavonoid contents of extracts are identified.
10. Research on preformulation
11. Making of anti-cancer pills
12. Tablets are assess
5. DRUG PROFILE

5.1 Curcumin:

![Chemical Structure of Curcumin]

**Chemical Information:**
- **Chemical Formula:** C21H20O6
- **Molecular Mass:** 368.385 g/mol

**Pharmacokinetic Data:**
- **Bioavailability:** 100%
- **Solubility:** Poor in soluble
- **Half-life:** 6 to 7 hours
- **Appearance:** Vibrant yellow-orange powder
- **Melting Point:** 183°C (361°F; 456 K)

**5.2 Description:**

Curcumin, a vibrant yellow compound, is synthesized by plants belonging to the Curcuma longa species. It serves as the primary curcuminoid found in turmeric (Curcuma longa), a member of the ginger family known as Zingiberaceae. This substance is marketed as an herbal supplement, an ingredient in cosmetics, a food enhancer, and a food dye. From a chemical standpoint, curcumin falls within the category of diarylheptanoids, specifically among curcuminoids. These are phenolic pigments responsible for imparting the characteristic yellow hue to turmeric. Despite its various applications, neither laboratory experimentation nor clinical research have substantiated any medical utility for curcumin. The compound is challenging to study due to its inherent instability and limited...
bioavailability. As a result, it is improbable to yield valuable insights for pharmaceutical development.

5.3 Structure Activity Relationship of Curcumin:

The Structure-Activity Relationship (SAR) of curcumin and its derivatives refers to the correlation between the chemical structure of these compounds and their biological activities. In the case of curcumin and its various derivatives, researchers study how specific modifications to the molecular structure affect their efficacy, potency, and interactions with biological targets.

Some key points in the SAR of curcumin and its derivatives include:

**Functional Groups:** Modifications or substitutions of functional groups in curcumin's structure can lead to changes in its activity. For instance, altering the phenolic groups may affect antioxidant or anti-inflammatory properties.

**Substituents:** Adding or changing substituents on the curcumin molecule can influence its bioactivity. Different substitutions can enhance solubility, stability, and binding to target proteins.

**Conjugation and Ring Modifications:** Changing the conjugation pattern or modifying the aromatic rings can impact biological activity. These alterations might affect the compound's ability to interact with enzymes, receptors, or other biomolecules.

**Stereochemistry:** Isomeric forms of curcumin may have varying effects due to differences in spatial arrangement. Stereochemistry can influence how a molecule interacts with enzymes or receptors.

**Bioavailability Enhancements:** Many studies focus on modifying curcumin's structure to improve its bioavailability, as the native form has limited absorption. Derivatives might include delivery systems, nanoparticles, or prodrugs.

**Target Specificity:** Structural modifications can lead to derivatives with improved selectivity for specific molecular targets, potentially reducing off-target effects.

**Toxicity and Safety:** Altering the structure of curcumin can impact its toxicity profile. Some modifications might enhance safety or reduce potential adverse effects.

**Pharmacokinetics:** Changes in the structure can influence the compound's absorption, distribution, metabolism, and excretion, affecting its overall pharmacokinetic profile.

**Synergistic Effects:** Combining curcumin derivatives with other compounds might lead to
synergistic effects, enhancing therapeutic outcomes. Research in this field aims to optimize curcumin derivatives for various applications, such as drug development, nutraceuticals, and medical treatments. By understanding how structural changes influence biological activities, scientists can design derivatives with improved properties and potentially unlock new therapeutic avenues.\[^{90}\]

### 5.4 Excipients Profile:

Most of the excipients selected are widely used in oral pharmaceutical formulations and are GRAS listed, sourced from reputed international manufacturers. All the excipients are from BSE-TSE free sources. A confirmation stating that excipients do not contain and are not derived from specified risk materials as defined in current commission directives was taken.

Following is the list of excipients in the final formulation.

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcuminoid (Curcumin Extract)</td>
<td>Rhizome Active Content</td>
</tr>
<tr>
<td>Mequinol</td>
<td>Filler</td>
</tr>
<tr>
<td>Turmerine</td>
<td>Enhancing Agent</td>
</tr>
<tr>
<td>Piperine</td>
<td>Enhancing Agent</td>
</tr>
<tr>
<td>peptides</td>
<td>inhibit tumour cell proliferation or migration, or suppress the formation of tumour blood vessels</td>
</tr>
<tr>
<td>Gum Acasia</td>
<td>Stabilizer, Emulsifier, Thickener</td>
</tr>
<tr>
<td>Starch</td>
<td>Binding Agent</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Lactose</td>
<td>Diluent, Binder</td>
</tr>
</tbody>
</table>

**Curcumin Nonproprietary Names:**

Diferuloylmethane, Curcuma Longa, Turmeric Root, Wild Curcuma, Curcuma, Curcuma
aromatica
6.EXPERIMENTAL WORK

6.1 MATERIALS USED

The Materials employed in the formulations and evaluations and the corresponding suppliers were listed in the following Table No.6.1.

Table No.6.1: List of Materials Used

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>MATERIALS USED</th>
<th>SUPPLIER</th>
<th>ROLE OF MATERIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Curcumin</td>
<td>Noida, Uttar Pradesh, India</td>
<td>Rhizome Active Content</td>
</tr>
<tr>
<td>3.</td>
<td>Turmerine</td>
<td>K PATEL PHYTO EXTRACTIONS PVT. LTD.</td>
<td>Enhancing Agent</td>
</tr>
<tr>
<td>5.</td>
<td>Peptides</td>
<td>Core Peptides</td>
<td>Inhibit tumour cell proliferation or migration, or suppress the formation of tumour blood vessels</td>
</tr>
<tr>
<td>6.</td>
<td>Lactose</td>
<td>Shreeji Pharma International</td>
<td>Diluent, Binder</td>
</tr>
<tr>
<td>7.</td>
<td>Starch</td>
<td>Natural Ingredient</td>
<td>Binding Agent</td>
</tr>
<tr>
<td>8.</td>
<td>Magnesium Stearate</td>
<td>Global Calcium</td>
<td>Lubricant</td>
</tr>
</tbody>
</table>

6.2 EQUIPMENTS USED

Table No. 6.2: List of Equipment Used
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Equipment's/Instruments</th>
<th>Manufacturer/Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Electronic Weighing Balance</td>
<td>Electronic balance, Shimadzu, Japan</td>
</tr>
<tr>
<td>2.</td>
<td>Sieves</td>
<td>Hicon sieves</td>
</tr>
<tr>
<td>3.</td>
<td>Hot air oven</td>
<td>Hicon</td>
</tr>
<tr>
<td>4.</td>
<td>Vernier caliper</td>
<td>Mutitoyo, Japan</td>
</tr>
<tr>
<td>5.</td>
<td>Hardness tester</td>
<td>Monsanto hardness tester</td>
</tr>
<tr>
<td>6.</td>
<td>Friability apparatus</td>
<td>Model-EF-2W, Electrolab</td>
</tr>
<tr>
<td>7.</td>
<td>Tablet compression Machine</td>
<td>Fluid pack</td>
</tr>
<tr>
<td>8.</td>
<td>Dissolution Apparatus</td>
<td>Electro lab, DT (UST)</td>
</tr>
</tbody>
</table>

6.3 Selection of the Plant: Drawing upon an analysis of existing literature, extensive consultation with medical professionals, and under the guidance of Dr. Rajesh Mujariya, the plant Curcuma longa is chosen for analysis of the anticancer activities.

6.4 Authentification of the Plant: The Curcuma longa plant material was collected in April to July from the Botanical Garden of Balaghat, and verified by Dr. Rajesh Mujariya, Director of the Institute of Pharmaceutical Science & Research (IPSR). Each plant has a voucher specimen that has been kept for future reference.

6.5 Preparation of Crude Drug for Extraction: Selected plant rhizomes and roots were used to prepare the extract. Selected plant rhizomes and roots were collected and dehydrated in the shade. Rhizomes and roots were dried and then crushed mechanically into a coarse powder. Then sieve No. 16 was used to sift this coarse powder of chosen plant Rhizomes and Roots. And after passing, that was kept for extraction in an airtight container.

6.6 Physico-chemical Evaluation: Plant Rhizomes and Roots that had been dried and stored as a powder underwent a standard procedure to determine various types of physicochemical parameters.

6.6.1 Determination of Ash Values:
Ash values recognition is designed to identify inexpensive goods, expired medications, and sand or other earthy materials. By utilizing water-soluble ash and acid insoluble ash, it can also be employed as a method of differentiating the chemical components (Ministry of Health and Family Welfare, 1999).

6.6.1.1 Total Ash Value: Using a silica crucible that has been weighed beforehand, 5 grams of meticulously measured air-dried powder extracted from selected plant rhizomes and roots were
incinerated until all carbon content was eliminated. To determine the percentage of total ash concerning the air-dried powdered plant materials, the mixture's weight was taken after it cooled down, following the guidelines outlined by the Ministry of Health and Family Welfare in 1999.

6.6.1.2 Acid Insoluble Ash: Utilizing 25ml of hydrogen chloride (HCl) that has been diluted, the ashes obtained from the chosen plants were subjected to a 5-minute heating process. The residual waste was collected onto filter paper that is devoid of ash particles. This collected material was then rinsed with hot water, ignited, and subsequently weighed. By comparing this weight against the weight of the air-dried medicinal substance, the percentage of acid-soluble ash was calculated following the guidelines provided by the Ministry of Health and Family Welfare in 1999.

6.6.1.3 Water Soluble Ash: The ash derived from the plant material was subjected to heating in 25 cubic centimeters of water for a duration of 5 minutes. The resulting waste was collected onto filter paper that is free from ash content. Subsequently, this collected residue was rinsed with hot water that had been heated to the point of ignition. To determine the quantity of water-soluble ash contained within the air-dried medicinal substance, follow the procedures outlined by the Ministry of Health and Family Welfare in 1999.

6.7 Determination of Extractive Values:

6.7.1 Soluble Extractive: The procedure involved utilizing 100 milliliters of various solvents, including petroleum ether, ethanol, hydroalcohol, and distilled water. In a secure flask, 5 grams of roughly powdered, air-dried medicinal material was subjected to maceration using these solvents for a duration of 20 hours. Following this, the mixture was allowed to stand undisturbed for an additional 15 hours after having been shaken for 5 hours. From the resulting mixture, 25 milliliters of filtrate were placed in a shallow, flat-bottomed dish and subjected to evaporation until it reached dryness. The dried material was then heated to 105 degrees Celsius and weighed. By comparing this weight to the weight of the air-dried medicinal substance, the percentage of soluble extractive was determined. These steps were carried out in accordance with the guidelines provided by the Ministry of Health and Family Welfare in 1999.

6.8 Extraction of dried Rhizomes and Roots by using various solvents of increasing polarity:

The extraction process used Curcuma longa's gathered, orderly, and ground Rhizomes and Roots. The Soxhlet apparatus has 500 g of powder placed into it equally. Following that, it was extracted using a range of non-polar to polar solvents, including petroleum ether, ethanol, hydroalcoholic, and distilled water. Prior to usage, these solvents were refined. Consistent hot percolation with various solvents was used as the extraction method for 72 hours. By vacuum distillation, the extracts were concentrated to a volume of 1/10, which was then transferred to a 100ml beaker and evaporated with a water bath. It was cooled and then put in a desiccator to draw out the excess moisture. Further
research was conducted using the dried extracts, which were stored in airtight containers.

6.9 Preliminary phytochemical studies:

6.9.1 Tests for Flavonoid:

1. When sodium hydroxide solution to a small quantity of extracts resulted in the appearance of a yellow to orange coloration, indicating the presence of flavonoids.

2. A small portion of the extracts was treated with concentrated sulfuric acid, and the emergence of a yellow-orange color indicated the presence of flavonoids.

3. Shinoda’s Test: alcohol was introduced to a small amount of extracts, and after allowing it to dissolve, a fragment of magnesium was introduced. Subsequently, concentrated hydrochloric acid was added drop by drop, and the mixture was subjected to heating. The presence of flavonoids was signified by the manifestation of a bright yellow color.

6.10 Determination of total flavonoid content:

The total flavonoid content of the sample was assessed using the colorimetric technique involving aluminum chloride. Quercetin was employed to establish a standard calibration curve for quantifying the total flavonoid concentration. Serial dilutions of quercetin with methanol (ranging from 5 to 250 µg/mL) were used to create standard solutions, starting from a stock solution containing 5.0 mg of quercetin in 1.0 mL of methanol. For each sample, 0.6 mL of a 2% aluminum chloride solution was mixed with 0.6 mL of the extracts (100 µg/mL). This mixture was then left at room temperature for 60 minutes. The absorbance of the reaction mixtures was measured at 420 nm, compared against a blank. Utilizing the calibration curve, the total flavonoid content in the samples was calculated, expressed as milligrams of quercetin equivalent (QE) per gram of dry plant material. The readings were averaged after being recorded three times.
7. EXPERIMENTAL DETAILS

7.1 Preformulation of Herbal Tablet:

7.1.1 Angle of Repose Determination:

The angle of repose was determined using the funnel method. Precisely weighed granules were introduced into a funnel, allowing them to flow freely onto a surface. The diameter and height of the resulting powder cone were measured, and the angle of repose was calculated using the following formula:

\[ \tan \theta = \frac{h}{r} \]

Where:

\( \theta \) represents the angle of repose,
\( h \) stands for the height of the formed powder cone, and
\( r \) signifies the radius of the formed powder cone.

7.1.2 Loose Bulk Density Measurement:

The loose bulk density (LBD) was determined by introducing a precisely weighed quantity of granules into a graduated cylinder and measuring both the volume and mass. The loose bulk density was calculated using the formula:

\[ \text{LBD} = \frac{\text{Weight of the Powder}}{\text{Volume Occupied in the Cylinder}} \]

7.1.3 Tapped Bulk Density Measurement:

The tapped bulk density (TBD) was determined by introducing a known quantity of granules into a graduated cylinder. The cylinder was subjected to tapping using a mechanical tapping apparatus. Tapping was continued until there was no further change in volume observed. The tapped bulk density was then calculated using the formula:
TBD = Weight of the Powder / Volume of the Powder after Tapping

7.1.4 Hausner Ratio Calculation:

The Hausner ratio provides insight into the frictional resistance of the drug. It is calculated using the following formula:

\[ \text{Hausner Ratio} = \frac{\text{TBD}}{\text{LBD}} \]

7.1.5 Carr's Compressibility Index Calculation:

The Carr's compressibility index is a parameter that helps assess the compressibility of the material. It is calculated using the formula:

\[ \text{Compressibility Index (\%)} = \frac{(\text{TBD} - \text{LBD}) \times 100}{\text{TBD}} \]

7.1.6 Loss on Drying Determination:

To assess the loss on drying (LOD), a glass stoppered bottle was employed. Precisely 1 gram of granules was weighed and added to the bottle. These bottles were then positioned within a drying chamber. The stopper was removed from the bottle, and the contents were dried for a specified duration until a constant weight was achieved. The calculation of loss on drying was carried out using the formula:

\[ \text{Loss on Drying (\%)} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100 \]

This methodology is in accordance with the approach described by Lachman et al. in 1987.

7.2 Synthesis of Curcumin:

In 1918, Lampe released the initial study regarding the creation of curcumin, one hundred years after its extraction from turmeric. Lampe's process involved five steps and began with the utilization of carbomethoxy feruloyl chloride and ethyl acetoacetate. Subsequently, Pabon introduced a simplified technique to produce substantial amounts of curcumin. This method involved combining acetylacetone with substituted aromatic aldehydes in the presence of boron trioxide (B2O3), trialkyl borate, and n-butylamine. Several research groups have since employed this procedure with slight modifications for subsequent curcumin production. In attempts to enhance yields, certain patents propose the use of unreactive organic amide solvents, B2O3, trialkylborate, and n-butylamine. Efforts to substitute boron oxide with boric acid proved unsuccessful. Rao and Sudheer suggested trifluoroboronite, leading to the creation of stable curcuminoid trifluoroborononites that could be converted into curcumin through hydrolysis in aqueous methanol with a pH of 5.8. The pivotal step in each of these processes is the interaction between 2,4-diketones and appropriate aromatic aldehydes.\[^{91}\] Complexing it with boron prevents the diketone from participating in Knoevenagel condensations. Optimal conditions for these reactions involve anhydrous settings and polar aprotic solvents, facilitating the separation of curcumin from the reaction mixtures. Primary and secondary amines serve as catalysts to provide the necessary basicity for deprotonating the diketone's alkyl
Scavengers like alkyl borates are employed to eliminate the water formed during the condensation reaction, which could hinder curcumin production. Under slightly acidic conditions, the boron complex disassembles into curcumin. The curcumin from this reaction mixture can be extracted through column chromatography after repetitive precipitation and washing, illustrates the comprehensive reaction scheme employing the Pabon approach.

![Reaction Scheme](image)

Figure 7.1 Production of curcumin using the general technique presented by Pabon

### 7.3 Characterization of Pure Drug (Curcumin):

The pure drug has been extensively characterized based on a range of parameters, showcasing robust attributes such as potent antioxidant, anti-carcinogenic, anti-inflammatory, anti-angiogenic, antispasmodic, antimicrobial, anti-parasitic, and various other beneficial activities.

#### Sample Preparation:

#### Formulation Development:

The wet granulation method was chosen for tablet formulation due to its suitability for small-scale formulations. This method offers ease of implementation and is well-suited for creating consistent and uniform tablet formulations on a smaller scale.

#### Process:

- Curcumin extract and other excipient was weighed, ground, and separately run through an 80-number sieve.
- All materials other than talc and magnesium stearate were combined and ground in a pestle and mortar before being once again put through sieve number 80.
- After combining the extract with the starch/acacia solution, the lump was created.
- Lump was screened over sieve number 18 to obtain granules, which were then dried in a Hoover dryer at 35°C.
- Add talc and granulated magnesium stearate.
- To eliminate larger granules, the granules were once again processed through sieve number 18 before being placed in desiccators.
After that Compressed that granules into desired punching machine to give proper shape and size to the tablet.

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Curcumin Extract</td>
<td>450</td>
<td>450</td>
<td>450</td>
<td>450</td>
<td>450</td>
<td>450</td>
</tr>
<tr>
<td>2</td>
<td>Lactose</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>starch</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Gum acasia</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Magnesium stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Talc</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Piperine</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Peptides</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Tablet weight 500 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.4 Evaluation of herbal tablet:

7.4.1 Uniformity of Weight: 20 pills from each formulation were chosen at random, and each one was weighed separately. The average weight of each tablet was determined and compared to it.

7.4.2 General appearance: During the evaluation process, the overall appearance of the tablet was assessed, including factors such as its color, odor, and texture.

7.4.3 Hardness test: To endure the mechanical stresses encountered during various handling operations, tablets must possess a specific level of strength or hardness, as well as resistance to friability. The Monsanto hardness tester measured the hardness of 20 randomly chosen tablets of each formulation.

7.4.4 Percentage friability test: The Roche Friabilator was employed to evaluate the friability of tablets. This involved determining the percentage of weight loss from a selection of 20 randomly chosen tablets from each batch. These tablets were subjected to tumbling within the friability machine. After rotating at a speed of 25 revolutions per minute for 4 minutes, the dust produced from the tablets was collected, and the percentage of weight loss was calculated.

7.4.5 Disintegration test: The disintegration time of the tablets was determined using a digital microprocessor-based disintegration test device (basket rack assembly, Lab India). Each individual tube was loaded with a single tablet, along with an accompanying disc. This assembly was then submerged in a 1000 mL beaker filled with water. The water level in the beaker was adjusted to ensure that the wire mesh was at least 25 mm above and below the water's surface at its highest and lowest points, respectively.
The equipment was maintained at a temperature of 37°C throughout the process. It was observed that all tablets uniformiment underwent disintegration and passed through the wire mesh in an equal amount of time.

7.4.6 Stability Studies: Environmental conditions like temperature, light, air, and humidity, along with packaging elements, can significantly influence the stability of a pharmacological dosage form. These factors can impact various stability parameters of the formulation. To assess the impact of these factors, all formulations underwent stability testing for a duration of 12 months. Long-term testing was conducted at temperatures of 25°C with a relative humidity of 60%, and at 40°C with a relative humidity of 75% for six months. During accelerated stability testing under elevated temperature conditions, several metrics were evaluated, including the tablets' color, odor, and texture, as well as average weight, hardness, friability, and disintegration time. These evaluations were performed to gauge the formulation's ability to withstand adverse conditions and maintain its intended properties over time.

8. RESULTS

8.1 Selection of the Plant: Insights from a comprehensive review of existing literature, extensive consultation with medical professionals, and under the guidance of Dr. Rajesh Mujariya, the plant Curcuma longa is chosen for analysis of the anticancer activities.

8.2 Physicochemical analysis of crude drug:

Table No. 8.1 Determination of Ash Values of selected plant

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Type of Ash</th>
<th>Percentage of Ash (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcuma Longa</td>
<td>Total Ash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acid Insoluble</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Water Insoluble</td>
<td>1.5</td>
</tr>
</tbody>
</table>

8.3 Determination of extractive value of selected plant:

Extractive Values are determined and reported in Table No.3

Table No. 8.2 Determination of extractive value of selected plant

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield of Curcuma Longa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petroleum Ether</td>
<td>34.2</td>
</tr>
<tr>
<td>Ethanol</td>
<td>38.9</td>
</tr>
<tr>
<td>Hydro Alcohol</td>
<td>42.6</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>41.0</td>
</tr>
</tbody>
</table>
8.4 Preliminary Phytochemical Evaluation of Selected Plant:

Chemical analysis of the phytoconstituents identified the presence of different phytoconstituents in diverse extracts. The results, which are presented in Table number 4, shown that the extract of Curcuma longa’s roots and rhizomes includes flavonoids.

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Tests</th>
<th>Curcuma Longa</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Petroleum Ether</td>
<td>Ethanol</td>
<td>Acetone</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Lead Acetate test</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Con.H2SO4 test</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Cl3 test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.5 Preformulation Studies of Curcumin:

Different granules’ angles of repose reveal outstanding flow characteristics between 25 and 29 degrees. The outcomes derived from the loose bulk density, tapped bulk density, Hausner ratio, and compressibility index values presented in Table 5 demonstrate favorable flow properties.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
<td>27.1</td>
<td>29.1</td>
<td>25.5</td>
<td>27.02</td>
<td>30.9</td>
<td>26.9</td>
</tr>
<tr>
<td>Loose bulk density (g/cm³)</td>
<td>0.78</td>
<td>0.78</td>
<td>0.77</td>
<td>0.75</td>
<td>0.77</td>
<td>0.76</td>
</tr>
<tr>
<td>Tapped bulk density (g/cm³)</td>
<td>0.9</td>
<td>0.9</td>
<td>0.89</td>
<td>0.88</td>
<td>0.9</td>
<td>0.89</td>
</tr>
<tr>
<td>Hausner ratio</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.17</td>
<td>1.16</td>
<td>1.16</td>
</tr>
<tr>
<td>Compressibility index (%)</td>
<td>13.04</td>
<td>13.1</td>
<td>13.6</td>
<td>14.3</td>
<td>14.3</td>
<td>14.1</td>
</tr>
<tr>
<td>Loss on drying (%)</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
</tr>
</tbody>
</table>

8.6 Evaluation of Herbal Tablet:

The tablets containing various extracts underwent testing across a range of parameters, and the results fell within the tolerance limits outlined by the Pharmacopoeia. The tablets demonstrated weight uniformity well within the acceptable 5% range. Notably, their hardness, varying from 6.98 to 7.02, indicates a considerable degree of solidity, suggesting they will be easy to dissolve. The mechanical stability of tablets is demonstrated by their low friability, which was determined to be between 0.36 and 0.47. The time it took for tablets to dissolve was 12–13 minutes, which was within Pharmacopoeia’s acceptable limit. Table No. 6 displayed all of the evaluation parameter results.
Table No. 8.5 Evaluation parameters of tablets of Curcumin

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of weight</td>
<td>1.03</td>
<td>1.45</td>
<td>1.49</td>
<td>1.79</td>
<td>1.50</td>
<td>1.60</td>
</tr>
<tr>
<td>Colour</td>
<td>Bright Yellow</td>
<td>Bright Yellow</td>
<td>Bright Yellow</td>
<td>Bright Yellow</td>
<td>Bright Yellow</td>
<td>Bright Yellow</td>
</tr>
<tr>
<td>Odour</td>
<td>Characteristic</td>
<td>Characteristic</td>
<td>Characteristic</td>
<td>Characteristic</td>
<td>Characteristic</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Texture</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>7.05</td>
<td>6.98</td>
<td>6.99</td>
<td>7.02</td>
<td>6.94</td>
<td>7.01</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.68</td>
<td>0.71</td>
<td>0.75</td>
<td>0.68</td>
<td>0.72</td>
<td>0.75</td>
</tr>
<tr>
<td>Disintegration time (minutes)</td>
<td>14.09</td>
<td>11.51</td>
<td>13.09</td>
<td>13.54</td>
<td>12.00</td>
<td>13.44</td>
</tr>
</tbody>
</table>
9. DISCUSSION

9.1 Selection of the Plant: Insights from a comprehensive review of existing literature, extensive consultation with medical professionals, and under the guidance of Dr. Rajesh Mujariya, the plant Curcuma longa is chosen for analysis of the anticancer activities.

9.2 Physicochemical analysis of crude drug: Physicochemical analysis was conducted on the powdered rhizomes and roots of the chosen plant. The assessment included the determination of ash values, encompassing total ash, acid-insoluble ash, and water-soluble ash. For the rhizomes and roots of Curcuma Longa, the findings revealed the following ash values:

- Total Ash: 8.3% w/w
- Acid Insoluble Ash: 3.7% w/w
- Water-Soluble Ash: 1.5% w/w

These values indicate the presence of a notable amount of inorganic matter in the samples, highlighting the mineral content within the plant material.

9.3 Determination of extractive value of selected plant:

Extractive Values of Curcumin are determined and reported.

9.4 Preliminary Phytochemical Evaluation of Selected Plant:

Chemical analysis of the phytoconstituents identified the presence of different phytoconstituents in diverse extracts. The results, which are presented and shown that the extract of Curcuma longa’s roots and rhizomes includes flavonoids.

9.5 Preformulation Studies of Curcumin:

The angles of repose for different granules demonstrated excellent flow characteristics, ranging between 25 and 29 degrees. Additionally, the results from measurements of loose bulk density, tapped bulk density, Hausner ratio, and compressibility index collectively suggest favorable flow properties for the granules.

9.6 Evaluation of Herbal Tablet:

The tablets containing a range of extracts underwent comprehensive testing across various parameters, and all results fell within the tolerance limits specified by the Pharmacopoeia. The tablets exhibited weight uniformity well within the acceptable 5% range. Notably, their hardness, spanning from 6.98 to 7.02, signifies a considerable level of solidity, indicating that they are likely to dissolve easily. The mechanical stability of tablets is demonstrated by their low friability, which was
determined to be between 0.36 and 0.47. The time it took for tablets to dissolve was 12–13 minutes, which was within Pharmacopoeia's acceptable limit. Table No. 6 displayed all of the evaluation parameter results.

In this study, curcumin was employed to assess anticancer activity; in the future, herbal tablets will also be used to assess their anticancer potency. The powerful active components from plant extract that are responsible for anticancer activity will be identified and isolated.
To research the spectrum against various forms of carcinomas, the anticancer efficacy of active ingredients against various cell lines will be examined.
Since all three of the researched plants have significant anticancer activity, a polyherbal formulation may be made to assess their synergistic effect. Comparative analysis can be done by comparing efficacy and potency in various formulations.

10. CONCLUSION

A well-formulated curcumin tablet was successfully developed using the following composition:
Active Ingredient: Curcumin
Lubricant: Starch
Binding Agent: Magnesium Stearate
Thickener: Gum Acacia
Binder: Lactose
Filler: Mannitol
This formulation resulted in the creation of high-quality tablets containing curcumin as the active ingredient. To guarantee that the tablet formulation including curcumin tablet is superior, the deserving profiles of tablets containing curcumin and tablets containing curcumin tablet should be compared.

In recent years, there has been significant research into the potential anti-inflammatory, antioxidant, anticancer, and antiandrogenic properties of curcumin, the active ingredient in curcuma longa extract. Notably, curcumin has demonstrated substantial anticancer benefits in both in vitro and in vivo studies involving various types of cancer such as prostate, breast, colorectal, pancreatic, and head and neck cancers. Clinical trials with human subjects have also shown its effectiveness and safety in treating cancer either alone or in combination with other anticancer drugs. Curcumin is believed to act through multiple mechanisms, potentially modulating the production of specific cytokines, enzymes, and growth factors, as well as influencing various cellular pathways including MAPK, EGF, NF-B, PKD1, COX-2, STAT3, TNF-, and I-K.

However, curcumin's limited water solubility, which results in poor oral bioavailability, cellular absorption, and chemical stability, has hindered its anticancer application. Various strategies, such as drug delivery systems and structural modifications, have been developed to overcome these limitations. The core pharmacophores responsible for curcumin's biological activity are the hydrogen donor group, -diketone moiety, phenyl rings, and their substituents. Chemical modifications have been performed on these moieties to produce derivatives of curcumin with improved water solubility and stability. Natural or synthetic polymers, lipids, and proteins have been used as carriers to enhance curcumin's stability and uptake by cancer cells, resulting in enhanced anticancer effects.

Curcumin's chemical structure may seem simple, but its chemistry is becoming increasingly complex as scientific understanding grows. Its natural form is symmetric and vibrant yellow, but it turns deep crimson in a basic pH solution. Curcumin is prone to degradation in aqueous and aqueous-organic solutions, especially in the presence of sunlight. Its metabolites differ from its degradation products, involving enzymatic O-conjugation and reduction steps. Interestingly, the synthesis of metabolic products is more challenging than that of degradation products.

Curcumin's unsaturated structure enables it to participate in nucleophilic addition reactions with protein thiols and selenols, which play roles in regulating cellular oxidative stress. Whether these reactions occur under physiological conditions is still debated. Further research is needed to clarify the kinetics and mechanisms of these reactions and their significance in curcumin biology. Research into curcumin-metal complexes has increased due to the effective metal-chelating nature of the -diketo moiety. While curcumin's complexation with metals decreases metal toxicity in living systems, the precise role of these complexes in curcumin biology remains unclear. The structure-activity analysis of curcumin-metal complexes in solution requires in-depth investigation.

Natural biopolymer formulations offer promise in addressing curcumin's bioavailability issues,
potentially enhancing its use in nutritional products. Additionally, curcumin conjugates with metal and metal oxide nanoparticles are being explored, showing potential applications in nanomedicine and targeted hyperthermia in cancer cells. These formulations are also being considered as MRI contrast agents and diagnostic tools for Alzheimer's disease. Despite considerable progress in curcumin's chemistry, there is still significant potential for chemists to harness this remarkable natural substance for medicinal purposes in treating various chronic conditions.

11. SUMMARY

This thesis examines the effectiveness of curcumin against breast cancer and provides a compelling case for their value as cancer preventatives. Given that free radicals are one of the main causes of malignancy, phytochemical analysis of the chosen plants confirms the presence of compounds like flavonoids, phenolic compounds, tannins, alkaloids, phytosterols, triterpenoids, etc. that possess strong antioxidant activity. In an anti-cancer study using certain plant extracts, it was discovered that given extracts at a dose of 500 mg/kg significantly decreased tumour size, tumour weight, body weight, and brought back the hematological parameters to essentially normal values. Selected plant extracts have the ability to prolong the lives, making potential therapy options for such a deadly sickness. Such groups treated with plant extracts experience alterations in neutrophil and lymphocyte counts as well as a greater likelihood that their hemoglobin, WBC, and RBC counts will return to normal, demonstrating the protective properties of the extract hematopoietic system.
12. REFERENCE


