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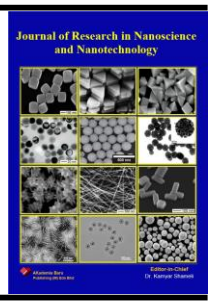

Curcumin Extract Loaded with Chitosan Nanocomposite for Cancer Treatment

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ABSTRACT

Cancer has become the root of problems in this era especially during this modern medicine time and because of that anticancer treatment had been developed to cure the patient suffering from this disease and for that an adoption of curcumin extract becomes a great deal of interest because of its anticancer properties. A recent study had been done aimed at determining the potential anticancer properties by chitosan in nanoparticle form. Furthermore, curcumin's weak water solubility enables it to accumulate in high concentrations, lowering its permeability to the cell. Curcumin is reduced via a variety of methods. With improving medicinal and research capabilities, nowadays the nano-pharmaceutics became an important field of science to develop an improve efficacy of different drugs specifically that target cancer diseases. In the present review, we focus on the plant extract of curcumin from Curcuma Longa plant and chitosan which derived from chitin in the exoskeletons of crustaceans which then be encapsulated into a nanocarrier formulation that can overcome this cancer. Thus, curcumin's potential preventative and therapeutic applications, as well as several forms of bio-nanocarriers that can be employed to effectively deliver curcumin to various target areas, will be reviewed.

Keywords:
Curcumin extract, green synthesis, chitosan nanoparticles, crosslinked, cancer treatment

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1. Introduction

Plants and herbals have been a great source of medicine especially in traditional practices where medicine in rural countries become scarce and hard to access because of it high cost and time consuming, while the plant derivatives have lots of properties which can be a study of scientific

purposes and become an important for medicinal pharmaceutical production [1]. However, cancer had been emerged as one of the most difficult diseases to cure with the deaths of millions since many years ago. This is because the disease had lots of factorials with uncontrolled division of cellular and metastasis, which is the way the cancer cells spread from place where they first formed to another part of the body [2]. One of the highest mortality rates for cancer disease in both males and females is the colorectal cancer [3]. Until this day, chemotherapy is the only method to eliminate the carcinogenesis process inside the body by following stages of progression and promotion [4]. Traditional cancer chemotherapeutic drugs have several drawbacks, including non-specific biodistribution and targeting, lack of water solubility, poor absorption, and low therapeutic indices [5]. Nanotherapeutics may be a viable option for overcoming these constraints. Medications can be placed onto nanometric carriers of the right size and surface properties, and they can then carry and deliver these drugs specifically and selectively to the target locations [6]. The small size of a nanoparticle drug delivery method aids passage via minute capillary arteries and avoids fast clearance by phagocytes, allowing for a longer circulation duration in the blood stream [7]. It has controlled release properties and can improve the efficacy of medications while also reducing hazardous side effects [8].

Therefore, from this review paper, detailed study will be focused on the curcumin extract which then the chitosan nanoparticles will be crosslinked with an agent TPP in the hopes of creating a new therapeutic drug which has anticancer properties. Other than that, it is also that from this review paper it can provide a good understanding on the methods achieved from this research and give valuable information in studying the curcumin extract and chitosan nanocomposite based on recent studies that had been done before.

2. Plant Extract

2.1. Overview of Medicinal Plants used in the Treatment of Cancer

Plants produce a variety of chemical substances that don't appear to play a direct part in their growth. Secondary metabolites are the name for these substances. These substances contain alkaloids, terpenoids, flavonoids, pigments, and tannins, among other things. Secondary metabolites have physiologic impacts on hematopoietic cells, lipids, and cardiovascular systems, including anti-inflammatory, anticancer, and contraceptive properties [9]. Finding secondary chemicals of natural goods and medicinal herbs has resulted in many advancements in popular cancer treatments. Plants are thought to have anticancer properties via suppressing cancer-promoting enzymes, mending DNA, boosting cell synthesis of antitumor enzymes, enhancing body immunity, and producing antioxidant effects [10]. The beneficial effects of plants in cancer treatment have been extensively researched and have yielded promising results. Furthermore, various studies and research have demonstrated the beneficial effects of plants in the treatment of diabetes, fertility and sterility, thyroid diseases, anemia, and psychological disorders. It's critical to find plants that can substitute chemotherapy and other time-consuming cancer treatments with cytotoxic effects [11]. As a result, it is desirable to have access to natural products that are more effective and have less adverse effects. 6 Medicinal herbs are significant for cancer treatment because they include a variety of chemical compounds that can be used to develop novel active materials against cancer.

2.2. Curcuma Species

Curcuma plants (Zingiberaceae family) are commonly used in traditional medicine to treat a variety of immune-related ailments. Many scientific investigations on their immunomodulating properties have been conducted to substantiate their ethnopharmacological use. The efficacy of six Curcuma species, namely *Curcuma longa L., Curcuma zanthorrhiza Roxb., Curcuma mangga Valeton & Zijp, Curcuma aeruginosa Roxb., C. zedoaria (Christm.) Roscoe, and Curcuma amada Roxb.*, and their bioactive metabolites to modulate the immune system, their mechanistic effects, and their potential [12]. An intensive literature search was conducted to obtain noteworthy results on these plants' immunomodulating properties. Curcuma species' immunomodulatory activities were examined, and future research tactics and perspectives on the plants as a source of new immunomodulators were considered. Most of the pharmacological studies used crude extracts of the plants to assess their immunomodulatory effects in vivo and in vitro. Chemically, the extracts were not described or standardized. The immunomodulatory effects of *C. longa* were the most studied of all the Curcuma species tested [13].

2.3. Extract Process of Curcumin from Curcuma Species

Though chemical methods can be used to produce curcumin, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) criteria allow curcuminoids isolated from natural sources to be used as food additives. Organic solvent extraction, steam distillation, hot and cold percolation, use of hydro-trope, and alkaline solution have all been mentioned in the literature as methods for extracting curcuminoids from natural sources. Several sophisticated approaches, such as supercritical fluid extraction, microwave-assisted extraction, ultrasound-assisted extraction, and enzyme-assisted extraction, have also been investigated [14]. These modern technologies for extracting natural biomolecules, such as ultrasonic, supercritical, and microwave-assisted extraction, are still in their early stages in India and have scaling concerns. As a result, it is vital to build a simple extraction process that uses little energy and occupies little space, as well as a simple setup that yields a sufficient extraction yield. Batch extraction of curcuminoids using ethanol as a solvent was proven in this study. Batch extraction of curcuminoids was also compared to a novel technique called three-phase partitioning, as well as the traditional Soxhlet method [15]. Although the exact mechanism is unknown to the researchers, key mechanisms for targeted protein partitioning have been proposed, including cosolvent precipitation, protein hydration changes, kosmotropic impact, isotonic precipitation, osmolytic, and salting out [16].

2.4. Curcumin

CUR in its physical form is in yellowed colour and has trait such as being hydrophobic and in its polyphenolic compound which is turmeric mainly extracted from a plant widely use and cultivated in Asian countries of *Curcuma longa* (*C. longa*) at the rhizomes [17]. One of the most essential challenges related with the administration of therapeutic drugs with low oral bioavailability is effective drug delivery. CUR is the active element in turmeric, however due to its limited water solubility, it has a low oral bioavailability [18]. The use of chitosan as a carrier for curcumin has been suggested to improve its water solubility and, as a result, its oral bioavailability. Furthermore, curcumin can also lower oxidative stress and regulate the expression of genes linked to oxidative stress and inflammatory responses [19]. Thus, because of its low toxicity, few side effects, and general

availability to a huge number of individuals, it is widely used to treat a variety of disorders. This experiment will be focusing on the physical targeting where there are two methods which is chitosan-based stimuli-sensitive nanoparticles and chitosan-based magnetic nanoparticles. From this information, we can learn on how to improve the delivery system of drug for curcumin depending on the stimulants such as pH, temperature, light, and ultrasound [20].

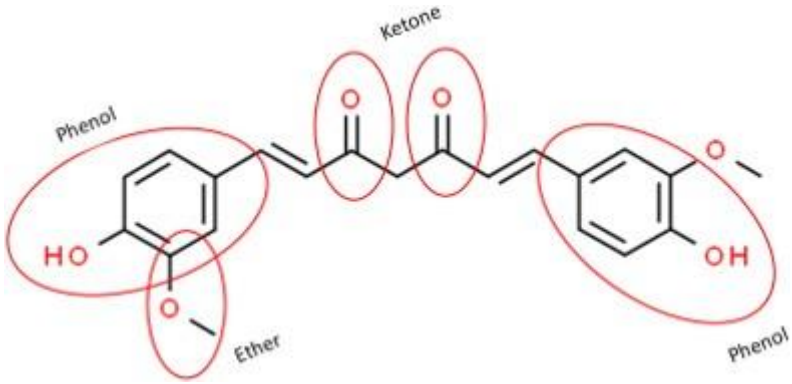

Figure 1. Chemical structure of Curcumin molecule.

Based on Figure 1, the CUR's structure can be studied to know its exact methods of action and properties that have yet to be fully explained, however recent research has indicated that it interferes with some of the signaling pathways involved in cancer and inflammation. Curcumin's molecular nature allows it to interact with a vast number of intracellular molecules, preventing the generation of free radicals [21]. During drug development, absorption, metabolism, and biodistribution in distinct tissues are only a few of the crucialfactors to consider. Acidic and alkaline hydrolysis, oxidation, and photodecomposition are all ways that curcumin degrades. Curcumin's pH-dependent degradation is faster in neutral to basic solutions, but it is known to be relatively stable at pH < 6.5 [22].

2.5. Application of Curcumin and Curcumin Derivatives in Cancer Treatment

CUR is the most common polyphenol component isolated from the rhizomes of *C. longa.* (turmeric). It was discovered for the first time in 1815 by two Harvard College Laboratory scientists, Vogel, and Pelletier. Since then, scientific interest in curcumin has grown, and its health benefits have been identified in increasing numbers [23]. Furthermore, CUR has been shown to offer therapeutic effects in a variety of chronic conditions, including inflammation, arthritis, metabolic syndrome, liver disease, obesity, neurological diseases, and, most importantly cancer [24]. Based on Figure 2, CUR appears to be a viable prospect as an effective anticancer medicine that can be used alone or in combination with other drugs in this scenario. It has an impact on a variety of signalling pathways and molecular targets that are involved in the development of various cancers [25]. The current review compiles the most recent research on curcumin's effects in the prevention and treatment of various malignancies.

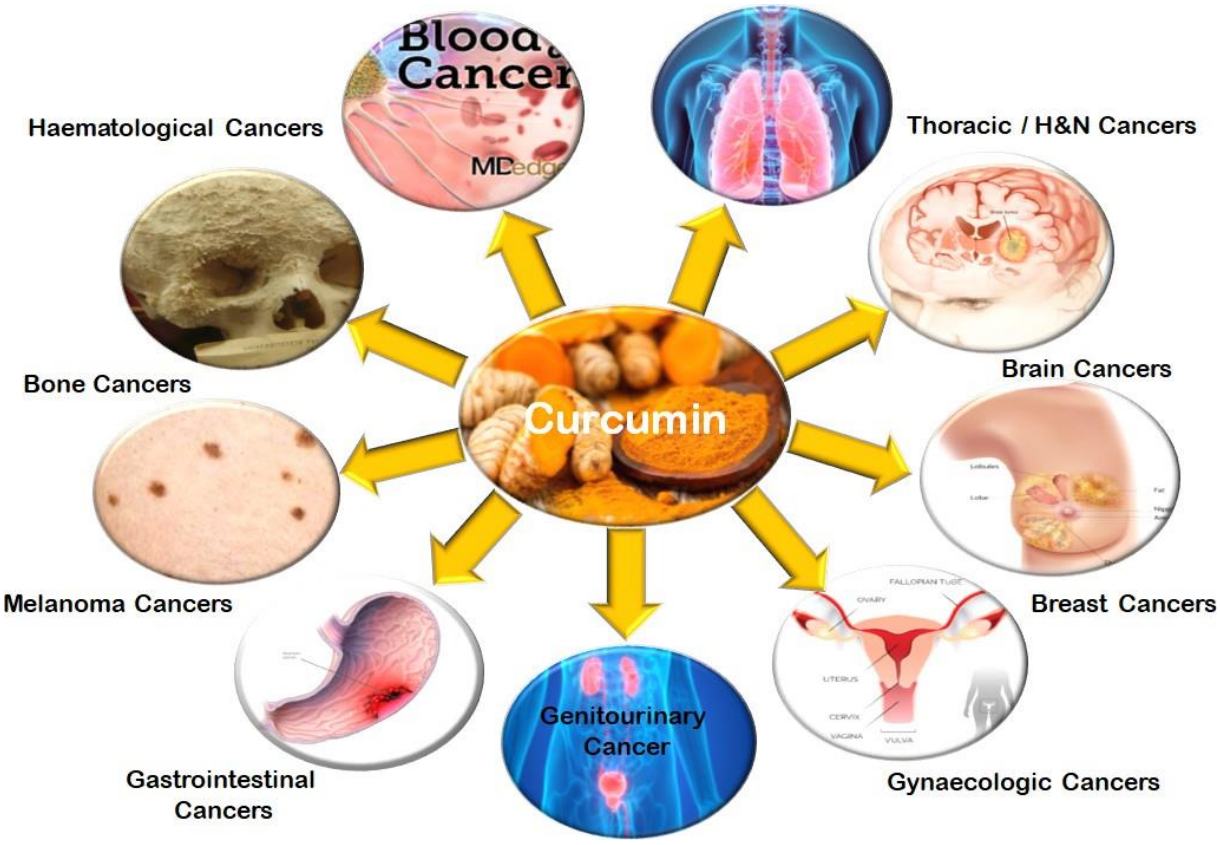

Figure 2. Targeting curcumin with several types of cancer.

According to (Table 1), several methods for extracting curcumin from fresh or dried turmeric root have been developed and refined, including extraction with solvents in microwaves, ultrasound, and supercritical fluids [26]. Curcumin derivatives can also be made through synthesis, with the most common method being Knoevenagel condensation, alternative microwave methods, or ultrasound irradiation [27]. However, chemicals extracted from natural sources with ethanol or propanol are preferable for culinary applications. As a result, extraction methods based on microemulsion extraction procedures were researched and optimised using green chemistry principles [28]. The studies' findings resulted in an increase in getting efficiency, a fall in product price, and the expansion of the market for its sale and derivative items.

Table 1. Methods for obtaining curcumin from ~~derivatives~~ *Curcuma Species.*

Turmeric Sample (Type of Species)	Methods	Particle Size of Turmeric Powder (mm)	Ref.
C. longa (dried turmeric powder)	Surfactant-free microemulsion	1.92	[2]
Curcuma longa (dried turmeric powder)	Soxhlet extraction ternary system	76.82-88.96	[4,6]
Curcuma longa (dried turmeric powder)	Ultrasound	67.15	[7]
Curcuma longa (dried turmeric powder)	Ultrasound/deep eutectic solvents	58.87	[7]
Curcuma longa	Microwave	88-105.3	[9]

(dried turmeric powder)			
Dried rhizomes of *Curcuma longa*	Supercritical fluid extraction	1.68	[10]
Curcuma aromatic Salisb	Soxhlet extraction	8.34	[11,12]
Curcuma aromatic Salisb	Supercritical carbon dioxide	7.54	[13]
Curcuma xanthorrhiza Roxb	Solvent extraction	4.98	[14]
Curcuma longa (dried turmeric powder)	Pressurized liquid extraction	0.125-0.45	[14]
Curcuma longa (fresh turmeric)	Solid phase	-	[15]
Curcuma longa (extract the essential oil)	Subcritical water extraction	90.19	[16]

2.3 Studies on Immunomodulatory Effects of Curcumin

Many studies demonstrate that inflammatory system dysfunction plays a major role in cancer development. Increased production of pro-inflammatory chemicals such as cytokines, reactive oxygen species (ROS), cyclooxygenase-2 (COX-2), transcription factors such as nuclear factor B (NFB), protein kinases B (AKT), activator protein 1 (AP1), signal transducer and activator of transcription 1 (STAT-1), STAT3 is a transcription factor that has a role in the start and progression of cancer [27,28]. Factor nuclear B is a pro-inflammatory transcription factor that regulates the production of proteins involved in several cell signaling pathways linked to cancer growth and inflammation, such as the cytokines interleukin (IL)-1, IL-2, and interferon (IFN) [29]. Phosphorylated NF-B attaches to DNA and begins oncogene transcription, which prevents apoptosis and promotes cellular proliferation and angiogenesis. Curcumin inhibits NF-B activity by inhibiting I kappa B kinase (IB) phosphorylation and nuclear translocation of the NF-B p65 subunit [30]. STAT3, a member of the STAT family, is a frequent target for various signaling pathways that regulate oncogenes and modulate the transmission of pro-inflammatory cytokines and growth factors [30]. This factor helps the cell develop and survive by raising the expression of anti-apoptotic proteins including Bcl-2 and Bcl-xL, which prevents apoptosis. Several factors have been identified as STAT3 activators, including IL-6, EGFR, PDGF, leukaemia inhibitory factor (LIF), oncostatin M, and the ciliary neurotrophic factor (CNTF) family of cytokines [31]. Furthermore, curcumin has been demonstrated to be a molecular target of STAT3 in numerous cancers, both directly and indirectly through IL-6 suppression [31]. Curcumin's immunomodulatory properties, on the other hand, are directed not only at molecular targets, but also at cellular components like macrophages, dendritic cells, and T and B lymphocytes [32].

3. Natural Biopolymers

3.1. Application as a drug carrier

3.2. Chitosan as a natural polycationic linear polysaccharide

After cellulose, chitin is the second most abundant biologically generated polymer on the planet [28]. It's the main structural component of shrimp, crabs, lobsters, and squid pens' exoskeletons, and it's also found in minor amounts in the cell walls of some fungi and yeast, as well as in plants [33]. The chemical structure of this polysaccharide is identical to that of cellulose, except the hydroxyl

groups at position C-2 have been replaced by acetamido groups [30]. When the degree of acetylation (DA, molar fraction of N-acetylated units) is less than 50%, Chitosan (CS) is produced primarily by partial deacetylation of chitin under high temperatures and alkaline conditions [33]. The skeleton of CS is formed by connecting glucosamine and N-acetylglucosamine via a 1,4-glycosidic link, resulting in a linear polymeric structure [33].

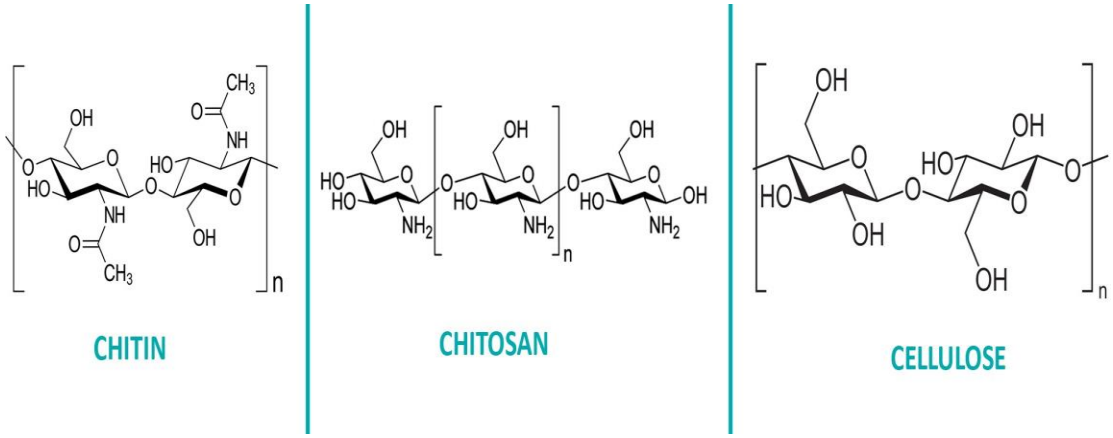

Figure 3 Chemical structure of (a) Chitin, (b) Chitosan, and (c) Cellulose.

Based on Figure 3, the molecular weight (Mw) and the DA of CS are the two most important structural characteristics that influence the polymer's overall behaviour as a biomaterial [34]. Commercially available CS with a wide range of DA and Mw (DA 35% and Mw between 10 and 800 kDa), with low Mw defined as less than 50 kDa, medium Mw defined as between 50 and 150 kDa, and high Mw defined as greater than 150 kDa [35]. Other than that, water, concentrated acid, alkali, alcohol, and acetone, as well as typical organic solvents, are all insoluble in CS. CS is a biocompatible and nontoxic polymer that has been widely explored for a variety of biomedical applications, including the formulation of small-scale drug delivery systems [36]. The polymer has mucoadhesive, haemostatic, chemo attractive, regenerative, analgesic, antioxidant, and immunomodulatory properties, which are largely related to its peripheral groups, particularly its primary amines and hydroxyl groups [36]. Its mucoadhesiveness causes brief opening of tight connections between epithelial cells of the intestinal mucosal barrier, allowing medicines, proteins, and dietary nutrition to pass through more easily [37].

CS is mostly found in insects, crustaceans, squid, algae, and fungi which were grouped into three based categories such as on molecular weight (low, medium, and high) [38]. CS with a high molecular weight has a longer chain and more hydroxyl groups. Other than that, it has a weak base that is water and organic solvent insoluble. However, under acidic conditions, chitosan is soluble in an aqueous solvent [39]. Due to its highly crystalline hydrogen bonds, CS's dissolution is poor, and its solubility in water or physiological conditions is low, limiting its application in drug delivery [40]. To circumvent its limitations as a drug delivery medium, chitosan is frequently chemically modified. CS- O-substitution (e.g., carboxymethylation) and N-substitution (e.g., reductive amination) can be utilised to build new covalent bonds, which can improve chitosan properties [41]. Furthermore, hydrogel formation forms covalent linkages with different crosslinkers to improve the drug distribution property of chitosan [42].

3.1 Cross-linked Chitosan Nanoparticles

Particulate chitosan structures are three-dimensional crosslinked networks in which crosslinkers connect polymeric chains. The crosslinking density is the most important factor in determining the qualities of a crosslinked NP, such as drug release and mechanical strength [43]. Nanoparticles are made primarily using four processes, depending on the desired chitosan structural properties which are covalent crosslinking, ionic crosslinking, polyelectrolyte complexation, and self-assembly of hydrophobically modified polysaccharide [44]. In general, chitosan nanoparticles are made by dropping the required crosslinker into the chitosan solution and stirring continuously for 1–24 hours, with or without moderate heating depending on the crosslinking chemistry [45]. These four techniques, as well as current delivery applications, are summarised and compared in Table 2.

Table 2. Cross-linked CS-NPs synthesis mechanisms.

Parameters	Covalent Crosslinking	Ionic Crosslinking	Ref.
Cross-linker Characteristics	Irreversible chemical linkers	Reversible ionic crosslinking	[29,30]
Main Interactions	Covalent bond interaction	Electrostatic interactions	[31]
Crosslinking Agents	Di-Aldehydes, Glutaraldehyde, Di / tricarboxylic acids	Tripolyphosphate (TPP)	[33]
Biocompatibility & Toxicity	Aldehydes are highly toxic, while natural carboxylic-based cross-linkers are considered biocompatible alternatives	Enhanced biocompatibility since the preparation of NPs by reversible ionic crosslinking, without the use of aldehydes and toxic cross-linkers	[34]
Particle Size	200-400 nm	100-350 nm	[34,36]
Drug Delivery Application	Toothpaste	Carrier of nanoparticles for anticancer drug	[36]

4. Cross-linked Chitosan/Curcumin Nanocomposite

4.1. Drug Release Kinetic

The therapeutic effects of these compounds are influenced significantly by the drug release. Because of their physicochemical features, different shapes and sizes of these nanocomposite have an impact on drug release. The chemical composition, MW, solubility, and crystallinity of the components that make up the NPs, as well as their ability to absorb water or the rate and rate of degradation, will all affect the NPs' release. Interactions between drugs or between drugs and polymers tend to have a substantial impact on drug release from the delivery mechanism [45]. Crosslinking with anions, precipitation, complex coacervation, modified emulsification, ionotropic glassing, precipitation-chemical glutaraldehyde crosslinking, and thermal crosslinking can all be used to make these nanocomposite drugs. The particle size, thermal and chemical stability of the drug molecule, reproduction of the kinetic release profile, stability, and residual toxicity of the finished product all influence the manufacturing method chosen [46]. Due of the solubility of chitosan, pH

affects the release of the medication from the chitosan and curcumin nanocomposite. Chitosan derivatives can tailor drug release to the medication's intended pharmacokinetic profile. Furthermore, the electrostatic interaction between protonated amine groups and H2O molecules was stronger at an acidic pH, causing chitosan polymers to dissolve, resulting in NPs matrix degradation and fast drug release [47]. The NPs swelled and even dissociated quickly, resulting in fast model drug release. Drug release could be faster at lower pH than at neutral or higher pH, based on the cumulative release of medicines.

The degree of crosslinking, the shape, the size, and the density of the particulate system, the physicochemical features of the drug, and the presence of an adjuvant in this study all influence drug release. In vitro release is further influenced by the dissolving medium's pH, polarity, and enzyme concentration [48]. The oral delivery system can be used to control the medication release from the chitosan and curcumin nanocomposite. Curcumin is released at the fastest con- centration in the simulated digestive system (pH 6.86), according to Liu et al., meeting the criterion of oral medication delivery.

4.2 Studies of the Delivery of Chemotherapeutic Drugs

Lipophilicity is one of the most important factors in determining cytotoxic drug uptake in cells, and it's also linked to the drug's pharmacokinetic profile and potency [46]. To be an optimum chemotherapeutic drug, there must be a balance between lipophilicity and hydrophobicity. In Figure 4, the transport of hydrophobic and hydrophilic conventional chemotherapy medicines was enhanced by chitosan [47].

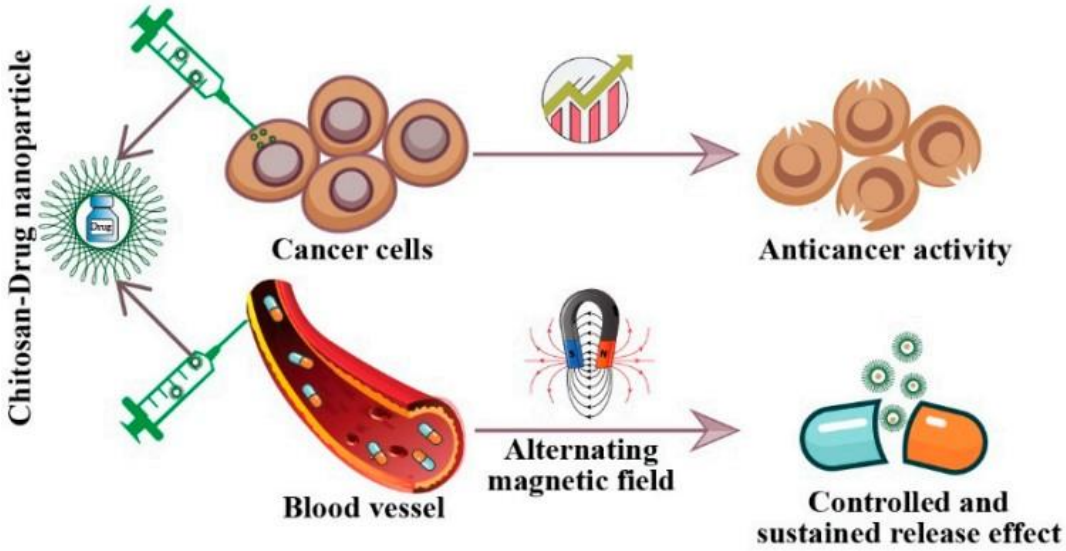

Figure 4 Using chitosan-based nanocarriers to deliver chemotherapy medicines in combination.

Doxorubicin (DOX) is a water-soluble chemotherapeutic medication that is used to treat a variety of cancers, including lung, thyroid, breast, and hematological malignancies [48]. Trastuzumab, which targets the Herceptin receptor, was subsequently added to the chitosan-DOX nanoparticles. When

compared to free DOX, trastuzumab-loaded chitosan-DOX (Tra-chitosan-DOX) nanoparticles showed stronger cytotoxic activity against SKOV3 ovarian cancer cells (Her2 positive) [49]. DOX loaded onto the surface of chitosan mesoporous magnetic nanoparticles (DOX-CMN) showed a controlled and sustained release effect of the drug in a different strategy. The use of an alternating current magnetic field boosted DOX release from DOX-CMN, enhancing DOX's cytotoxic action against MCF-7 cells [50]. Other than that, encapsulating DOX in a pluronic F127 polymer-chitosan micelle increased DOX's anticancer efficacy when compared to DOX that was not encapsulated.

5. Conclusions

Curcumin with loaded chitosan nanocomposite is a promising solution in improving the chances of treatment for cancer patients around the world. The studies of this short review paper consist lots of various applications, derivatives, and compounds for the chitosan as a carrier for plant extract to target the specific cancer cells inside the body. Therefore, the diversity of the composite materials depends on the purpose of use but for this study we focus on more on anticancer properties and ways for curcumin to play the role of additive that have the potential to fight these seemingly impossible-to-cure-disease. However, the way in which these nanomaterials can behave or influence human health must be considered, because given that they can be ingested or can cross the cell barrier by penetrating the skin – showing that Cur-NPs is versatile depending on their location inside the cell by specific mechanisms, it can damage the cell structure or even the DNA which eventually led to the death of the cells. Moreover, Cur-NPs is a green synthesis medicine by-product from the plant extract which is a highly sought-after treatment other than chemotherapy which can give a serious side effect to the cancer patient. In this moment, the proven fact that a safe and cheap method of getting treatment for cancer has made the medical industry took another huge step in securing the future of its people and free from cancer diseases.

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