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Curcumim in management of diabetic foot ulcer: A review

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***Abstract*---**Diabetic foot ulcers termed as DFUs or commonly known as diabetic injuries have become the significant reasons for mortality in patients who are suffering from diabetes. Curcumin, a polyphenol is the main curcuminoid present in turmeric (belonging to ginger family *Zingiberaceae*). It is largely utilized as a dietary, nutritional, herbal supplement, cosmetics element, shading specialist and coloring agent. Curcumin has intense calming, hostile, anti oxidant, anti inflammatory, antimutagenic, anticancer properties and features making it a commendable possibility for wound healing and other fiery sicknesses. It has been utilized worldwide in miscellaneous forms for manifold health benefits and has gathered noteworthy consideration in the beyond couple of time in treating diabetes and its complexities. Notwithstanding, not many examinations are accessible comparable to curcumin as a diabetic injury mending specialist with the fundamental components still in obscurity. Consequently, this paper examines the potential purposes of this potent natural compound curcumin for the treatment of DFUs with the comparing systems at various points of diabetic injury recuperating. The present audit likewise sums up the different in vitro and in vivo investigations laid out/provided details pertaining to curcumin in treating DFUs. It provide a concise summary of the plethora of research regarding role of curcumin.

***Keywords*---**curcumim, demethoxy curcumin, diabetic foot ulcers, turmeric, supplement.

Introduction

The WHO has distributed discoveries recommending the complete figure of individuals enduring with diabetes mellitus to have crossed a number of 347 million. In the year 2012 alone, the administration of diabetes in the USA touched up a bill of approximately $ 245 billion. Diabetic individuals were expected to have a 25% possibility of fostering chances of foot ulcer throughout their lifetime, a big part of which get contaminated, if left untreated, need to be removed. Consistently, roughly 83,000 lower appendage removals are performed because of DFUs, thereby connected with mortality in some cases. Because of an increase in number of diabetic's cases every year, the burden of its treatment is additionally ascending. The normal expense for curing tainted DFUs is observed to be USD 17,000, while a significant cost of its removal accounts for USD 45,000. These foot ulcers have become the significant leading reason for death cases in individuals with DM.

These foot ulcers occur as an outcome of various pathological conditions such as neuropathy, angiopathy and ischemia which becomes the major reason for infection. Existing treatment option centers around educating people about the disease progression, tolerant training, early finding, diagnosis and prevention. The present discrepancy in the medical services framework is with the end goal that harmless treatments are less successful and invasive therapy is quite costly. None of the current medicines can satisfy the generally obsessive prerequisites of foot ulcers and moreover, no single regime of combination drugs has been recommended in treating DFUs as of now. The potent polyphenol curcumin is the key bioactive substance in ginger spice (*Zingiber officinale*), broadly utilized as a nutritional supplement and for coloring purpose. Out of all the plant parts rhizome is mostly involved in the treatment of numerous ailments. Amongst the three curcuminoids present, curcumin is most conspicuous having a percentage of 77%, demethoxycurcumin and bisdemethoxycurcumin constitutes 17% and 3% respectively. Curcumin possess numerous health benefits which includes calming, hostile to oxidant, antiinfective, anti inflammatory, anti microbial, antimutagenic, angiogenic, anticancer and nerve recuperating properties. Thus, application of curcumin for the treatment of DFUs may not only aid in healing the injury, yet in addition synergize the general injury recuperating impact through different mechanisms. The present paper examines its potential in treating DFUs along with its mechanism of action involved at various periods of curing of injury in diabetes. Additionally, a rundown of the preclinical investigations performed with curcumin in it is incorporated to treat DFUs.

The present study emphasis on

- potential benefits of curcumin in treating foot ulcers along with its subsequent mechanisms involved at varied phases of diabetic wound healing.
- curcumin application as a bioactive agent.

Curcumin

Curcumin is the hydrophobic part which was segregated in 1815 quite interestingly, yet after around 158 years the substance was not really set in stone in 1973 by the scientist Roughly and Whiting (Roughley & Whiting, 1973). The compound design of curcumin comprises of two rings, which comprises of a methoxy ether bunch at the ortho position. Curcumin can easily solubilize in ethyl liquor, propylene glycol and cold acidic corrosive yet insoluble in water. Its maximum absorbance is observed at 425 nm. Curcumin is being documented as a non-hazardous synthetic for people because of many investigations (Shoba et al., 1998; Qureshi et al., 1992). Curcumin is liable for the beautiful yellow shade of turmeric. Its softening mark is 176-177°C, and it can make a rosy earthy colored salt with antacid (Braga et al., 2003).

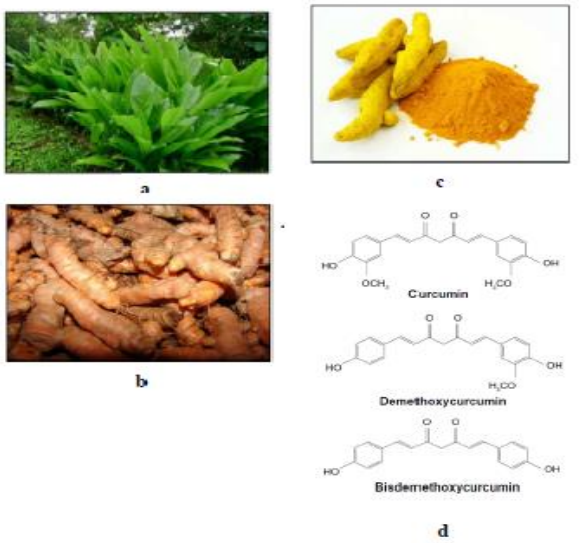

Figure 1 a: Turmeric plant, b: Turmeric rhizome, c:Turmeric powder (Palve and Nayak, 2012), and d: Chemical structure of the three curcuminoids (Aggarwal et al., 2003)

Pharmacological activity of curcumin

As per numerous clinical and preclinical examinations directed on curcumin during the previous many years, curcumin has been comprehensively recognized as a "wonder medication of things to come", because of its remarkable potential in forestalling and treating a few hopeless ailments (Epstein et al., 2010). Throughout the most recent 50 years, curcumin has been extensively researched for its anticancer properties. These investigations incorporated the impact of curcumin on bosom malignant growth colon disease, stomach problems, liver ailments and oral illness for which it can depict chemotherapeutic impacts. Different investigations incorporated the impacts of curcumin on illnesses like Alzheimer (Pan et al., 2008), gastric ulcer (Prucksunand et al., 2001), rheumatoid joint inflammation (Dcodhar et al., 2013), diabetes (Usharani et al., 2008), psoriasis (Heng et al., 2000), gut condition (Bundy et al., 2004) and HIV

(Balasubramanyam et al., 2004), which uncovered the capability of curcumin as a valuable remedial specialist. Further examinations have explored the impacts of curcumin on the cardiovascular framework, just as aspiratory and metabolic sicknesses additionally; studies showed the antimicrobial antiviral cancer prevention agent calming and wound healing impacts of curcumin broadly.

Few limitations of curcumin application as a bioactive agent. An ideal medication conveyance framework should be protected and convey the epitomized compound proficiently at the site of activity without displaying any antagonistic impacts. One more focal part of medication conveyance which ought to be thought about is the delivery properties of the framework, which is supposed to occur in a beneficial way to show better and effective results (Soppimath et al., 2001). An enormous number of examinations have researched the organic and pharmacokinetic attributes of curcumin in creatures, and less significantly in people (Epstein et al., 2010; Ghalandarlaki et al., 2014). Most of which have shown that the helpless dissolvability of curcumin in water has limited its maximum capacity since it confines bioavailability, security, and gastrointestinal ingestion. Consequently, a wide scope of exploration have been directed to work and focus on the pharmacokinetic features of curcumin in the previous a very long time by creating different definitions and designs to pass on it productively to the objectives (Ghalandarlaki et al., 2014).

Diabetes

Diabetes mellitus is a group of metabolic disorders characterized by constant infection and metabolic disorders portrayed by high inadequate blood glucose levels. In view of the insights, in 2010, 285 million individuals had diabetes and Shaw et al., (2010) further detailed in depth that this number would further rise to 439 million by 2030, which addresses a 54% increment. An assortment of elements will add to this significant increment including diminished actual work and exercise, obesity, maturing of the populaces and modernization of life style pattern. The previously mentioned figure which was expected for the occurrence of diabetes is evaluated to have a 42.4% ascent in North America, which was considered to be the most predominant region of the planet for diabetes occurrence in 2010, and 65.1% ascent in South, and Central America by the upcoming year 2030. Countries like Europe, Pacific, and South Asia are relied upon to encounter a 20, 47, and 72% augmentation in diabetes predominance, while Africa is anticipated to have an uncommon increment of 98 % in grown-ups by 2030. As per the review by Shaw et al., (2010) the diabetic populace will be obviously higher in agricultural nations by 2030 as the normal populace age will somewhat rise. Figure 11, looks at diabetes episodes in 2010 and 2013, in various regions of the planet.

Assuming that diabetes isn't as expected controlled, it may prompt different issues like obesity, stroke, coronary illness, diabetic retinopathy and diabetic nephropathy. Likewise, diabetes adds to various inconveniences affecting the foot which includes ulcer, osteomyelitis and Charcot's neuroarthropathy. As a clear indication by the writing, Australia's public wellbeing consumption on ongoing wounds, for example, foot ulcers is assessed to be roughly 500 million dollars each year (McGuiness & Rice, 2009). The chronicity of wounds has turned into a

significant issue not just as a result of the financial weight of the clinical expenses, yet in addition its effect on patients' enthusiastic prosperity and personal satisfaction (McGuiness & Rice, 2009). Henceforth, it is basic to lead further investigations in the field of constant wounds and their management to work on both financial and social parts of patients' lives.

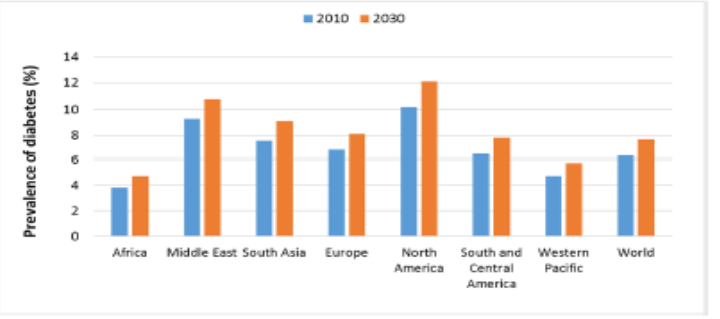

Figure 2 Prevalence of diabetes in the world in 2010 and 2030. Adapted from (Shaw et al., 2010)

Diabetic foot ulcer

While the grouping of healing happens deliberate and in a perfectly tuned design in intense wounds in the long run prompting wound conclusion, in diabetic wounds this interaction is disturbed and brings about non-healing wounds that are captured in, at least one of the previously mentioned stages (Falanga, 2005). Diabetic neuropathy can also be termed as nerve tissue harm, a typical complexity observed in diabetic patients, which is portrayed by an upgraded loss of fringe nerve filaments because of lessened flow of blood stream and raised glycemic levels (Dyck et al., 1993; Baši ć-Kes et al., 2011). It can happen in both diabetes type I just as type II, and is more regular in matured patients. Ordinarily, the manifestations of neuropathy arise 10-20 years following determination of diabetes and practically half of the cases of diabetes promote damage to nerves (Rathur & Boulton, 2005). While numerous patients are inclined to promotion this confusion even at beginning phases, others may never encounter it (Boulton et al., 2004). As indicated by a wide scope of studies, various variables add to the rise of foot ulcers. Vascular infections and ischemia disturb the healing system because of the diminished degrees of oxygen and supplements passed on to the harmed tissue (Guo & DiPietro, 2010). Likewise, upgraded nitric oxide levels, which leading to expansion in the development of ROS, alongside downregulation of glutathione and cysteine aggravate the situation and disable healing (Brem & Tomic-Canic, 2007). Also, unusual augmentation of the fiery stage starting from disabled articulation of development factors like TGF-β adds to this pathology (Tsunawaki et al., 1988). There are reports showing reduced creation of cytokines and macrophage brokenness, thusly prompting an impeded limit of macrophages to clean the wound site off of necrotic materials, which is fundamental for a legitimate and coordinated healing cycle (Khanna et al., 2010; Mirza & Koh, 2011; Robert Blakytny & Jude, 2009; Liu et al., 1999).

The variables which add to disabled healing in diabetes during the angiogenesis stage incorporate downregulation of hypoxia inducible component 1α (HIF-1α), which is liable for maintaining record of some development factors, for example, vascular endothelial development factor (VEGF), accordingly the degrees of VEGF will be decreased (Catrina et al., 2004; Botusan et al., 2008). An important concentrate by Pradhan et al., (2011) uncovered diminished articulation of a small number of other angiogenesis advancing development factors, such as, insulin like development factor 1 (IGF-1), platelet inferred development factor (PDGF), epidermal development factor (EGF) and interleukin-8 (IL-8), which animate cell proliferation, and relocation (Pradhan et al., 2011). A synchronized arrangement of ECM is critical during the time spent wound healing, as various endothelial cells move along these lines and use ECM as a framework while making fresh blood vessels during neovascularization. Subsequently, at last and most altogether, irrational movement of network metalloproteinases (MMPs), or downregulation of MMP inhibitors, address the most horrendous variables in diabetic wound healing interaction. MMPs can upset the healing system by separating development factors, just as ECM parts, for example, collagen, prompting ineffectively created ECM and thusly hindered re-epithelialisation and disabled the process of healing of lesions (Natrajan et al., 2015; Stricklin et al., 1993; Han et al., 2001). Figure 8 outlines the healing system in ordinary wound healing contrasted with the diabetic wound.

The clinical treatment of skin injury because of various extreme consumes or injury keeps on being a huge issue. A noticeable helpful specialist ought to have the option to increase at least one periods of the wound healing interaction without making unfavorable secondary effects.

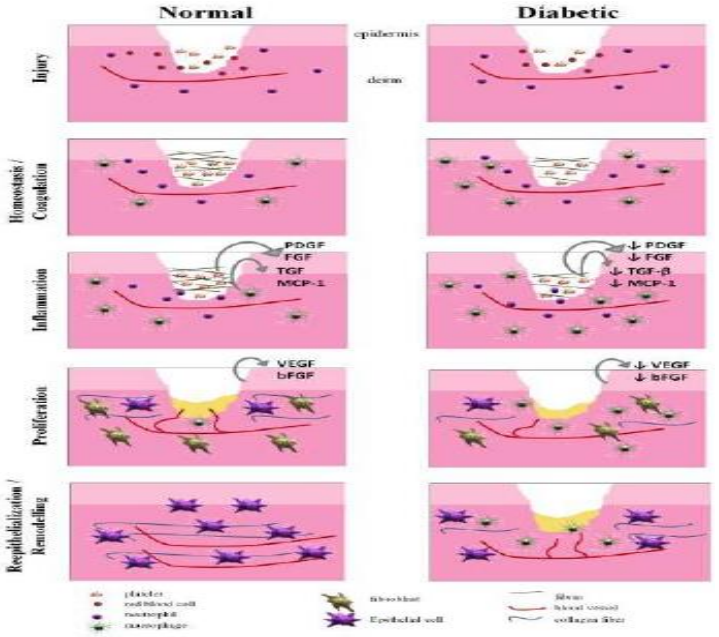

Figure 3.wound healing process in normal and diabetic wounds. Reproduced with permission from (Moura et al., 2013)

Influence of curcumin on the fibroblast proliferation

The presence of fibroblasts at the site of wound and harmed locales is of fundamental significance for the harmed tissue to be recuperated and recover. As per the concentrate by Blakytny & Jude, (2006), cutaneous wounds, which neglect to be healed in a fixed time-frame for the most part have hindered fibroblast propagation and relocation in the harmed region. The invasion and attack of fibroblasts into the harmed location is vital for granulation tissue arrangement/remodeling, collagen creation and remodeling.

A few examinations have depicted the beneficial outcome of curcumin on the invasion of fibroblasts entering into the wound region and researched the detailing of a curcumin-stacked polymeric gauze in a rodent model. The biochemical investigation uncovered upgraded and quicker wound decrease and expansion in cell proliferation of the examples. The sped up influence of the gauze was because of early execution of fibroblasts and their disconnection. In any case, there are impediments in the utilization of curcumin. On the contrary, it was observed that higher convergences of curcumin (25 μM) caused cell apoptosis turning oxidative, yet at lower focuses, positive outcomes were accomplished with next to no sign of cell passing.

Effects of curcumin on the stage of granulation tissue formation

Immediately after fourth day of any skin injury, new stroma or granulation tissue begins to develop. The interaction can be best described by the advancement of fresh little vessels and the invasion of fibroblasts, which aid in the arrangement of extracellular network. The recently framed tissue helps in appropriate relocation of the epithelial cells and wound conclusion and stress on re-epithelialization. It has been experimentally exhibited that the injury in rodents, which had been treated by COP (curcumin-stacked corrosive, oleic polymer) depicted a superior arrangement of granulation tissue 10 days post-treatment and simply a minor improvement just four days after any injury (Mohanty et al., 2012).

Effect of curcumin on the stage of collagen deposition

One more fundamental pre-imperative for the injured site to be mended in an appropriate period of time is the remodeling of the extracellular lattice, made up of various proteins, for example, collagen that can primarily adds upto 70-80 % of the skin. The last but not the least reason in the wound healing interaction is the foundation of scar tissue, which basically comprises of collagen filaments. Accordingly, the arrangement of sufficient amount of collagen and its statement add to fixing of wounds generally which showed that the substance of collagen expanded in rodent models which were undergoing treatment with curcumin wipe and that they were quite thicker and had been coordinated in more conservative lines contrasted with controls Likewise, one more concentrate showed not just an expanded measure of collagen in topically curcumin-treated wounds in rodents yet in addition that collagens had the option to develop quicker. One more aftereffect of this review was the increment in how much aldehyde in collagens, which can be a mark of the great cross-connected construction of the delivered strands. This seeing as additionally affirmed showed an expansion in level of

collagen just as a higher substance of aldehyde in a rodent model wound, treated with curcumin wrap contrasted with the control.

Conclusion

The crux can be enumerated as that this potent compound curcumin was proven to demonstrate numerous biological activities in treating serious complication of DFUs making it a worthy molecule. Various underlying mechanisms include inhibition of activity of matrix metalloproteinases and proinflammatory cytokines (TNF-α, IL-1β; decreased inflammation and ECM degradation). It also inhibits mitogen activated protein kinases and suppression of lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) up regulation (decreased nerve damage). Curcumin tends to increase the levels of anti-oxidant enzymes SOD, Glutathione peroxidase (GPx)) leading to decreased oxidative stress and eNOS causing decreased vascular occlusion. It also raise the levels of HO-1, VEGF, TGF-β1 which promote angiogenesis and SDF-1α, HIF-1α causing vasculogenesis. Besides these potential documented biological actions, clinical trials are only available for treating diabetic retinopathy, nephropathy and microangiopathy. Hence, further controlled studies should be certainly pursued in humans to obtain reliable results and prove the potential application of curcumin in DFU associated complications. Overall, the manifold biological activities of curcumin clearly indicate its usefulness and might become a probable candidate for various DFU-related complications.

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