

Curcumin: a novel non-steroidal contraceptive with antimicrobial properties

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1. ABSTRACT

Women face unique pathologies and challenges related to the female genital tract (FGT), including vaginal infections and gynecologic cancers. Vaginal infections faced by women include bacterial vaginosis (BV), vulvovaginal candidiasis (VC), and sexually transmitted infections (STIs). Curcumin, a component of the dietary spice turmeric, has immense biological properties, including antioxidant, anti-inflammatory/immunomodulatory, and anticancer effects. It has no side effects and is well-tolerated, making it an ideal treatment modality highly desired by women. Recently, our laboratory showed, for the first time ever, that curcumin exhibits a spermicidal and broad-spectrum microbicidal activity against several species of bacteria and yeast involved in vaginal infections. Thus, it could provide a novel, non-steroidal contraceptive having both spermicidal and microbicidal properties and can be panacea in women for treatment of several FGT pathologies, including gynecologic cancers.

2. INTRODUCTION

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), commonly known as diferuloylmethane, is the yellow pigment present in the rhizomes of turmeric (*Curcuma lownga*). Turmeric is a common dietary spice that has been used as an herbal remedy in Ayurvedic Indian medicine for thousands of

years. Curcumin was first isolated in its impure form in 1810, extracted in crystalline form in 1870, and its chemical structure was later elucidated in 1910 (1). Turmeric is not a “hot” spice, but rather a coloring material.

2.1. Versatile biological properties

Curcumin has immense antioxidant, anti-inflammatory/immunomodulatory, and anticancer properties against a variety of pathologies (1-3). Due to its pleiotropic actions, it is not surprising that curcumin affects countless intracellular signaling pathways. Several targets have been deciphered for various biological activities to decode the structure-function conundrum. Curcumin acts as an anti-inflammatory/immunomodulatory by interacting with several targets, including cyclooxygenase 2 (COX-2), lipoxygenase (LOX), inducible nitric oxide synthase (iNOS), nuclear factor (NF)- κ B, tumor necrosis factor (TNF)- α , interleukin (IL)-1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory enzyme (4-8). Its antioxidant properties have been attributed to modulation of several molecules, including nuclear factor (erythroid-derived 2)-like 2 (Nrf2), HO-1 (heme oxygenase-1), paraoxonase 1 (PON1), and antioxidant glutathione (GSH) (9-12). Its anticancer effects involve intervention at several stages of cancer development, cellular transformation, tumor initiation, tumor promotion, metastasis, and angiogenesis. Several targets have been delineated for anticancer effects

including caspase family proteins, human epidermal growth factor receptor 2 (HER-2), epidermal growth factor receptor (EGFR), activator protein 1 (AP-1), cyclin D1, B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xL), tumor proteins p53 and p210, c-Jun N-terminal kinase (JNK), protein kinase B (Akt/PKB), and AMP-activated protein kinase (AMPK) (13-15).

2.2. Unique molecular structure

The versatile biological effects of curcumin have been attributed to its ability to bind to various molecular targets, which stems from its unique molecular structure (16,17). It contains two ferulic acid residues joined by a methylene bridge, and has two hydrophobic phenyl domains connected by a flexible linker. Molecular docking studies show that curcumin can adopt many different conformations, allowing it to maximize hydrophobic interactions with a molecular target (18). Its phenolic and carbonyl functional groups located in the center and terminus can participate in hydrogen bonding, while its phenyl rings can participate in π - π van der Waals interactions with aromatic amino acid side chains (18). Curcumin exists in enolic and β -diketonic forms, but in solution primarily exists in its enolic form, which is important for its radical-scavenging activity (9). In enolic form, the molecule can both donate and accept hydrogen bonds from the midsection and act as a chelator of positively charged metals, which are often found in the active sites of target proteins (18,19). The keto-enol tautomerization of curcumin allows it to act as a Michael reaction acceptor to nucleophilic attack, thereby binding covalently to nucleophiles (20,21).

Curcumin is insoluble in water, but soluble in organic solvents such as DMSO (dimethylsulfoxide), ethanol, methanol, and acetone (22). Although the stability of curcumin increases in acidic pH, the solubility and bioavailability decreases in this pH range. At physiological pH conditions (37°C, pH 7.4.), 90% of curcumin degrades within 30 minutes (23). Curcumin also rapidly decomposes when exposed to sunlight, yielding degradation products which include trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal, vanillin, ferulic acid, and feruloyl methane (23). It has increased stability when supplemented by ascorbic acid, glutathione, and other antioxidants (9). As curcumin degrades rapidly in serum-free culture, the stability of curcumin in media is often improved by including 10% fetal calf/human serum (23). Curcumin is relatively poorly absorbed, rapidly metabolized, and quickly systemically eliminated *in vivo* (18). The bioavailability of orally digested curcumin is low due to relatively low intestinal absorption, rapid metabolism in liver, and elimination via gallbladder (9). It is mainly eliminated from the body via feces and some excretion via urine (9).

2.3. Lack of toxicity

While turmeric has been used in traditional medicine for thousands of years, the toxicity and

pharmacokinetic profile of curcumin has only recently been established.

Curcumin safety has been demonstrated in numerous *in vitro* cell systems, animal models, and humans (24). Curcumin has been tested in various normal human cells/cell lines *in vitro*, including bone marrow stromal cells (25), fibroblasts, and human esophageal, oral, and vaginal epithelial cells (26-28). It shows no toxicity.

The toxicity of curcumin has also been tested in several animal models, including rats, mice, and monkeys (29-31) delivered via various routes including oral, intravenous, intramuscular, and intraperitoneal. It shows no toxicity in the animal models tested or by these routes. In a recent study conducted in our laboratory, the curcumin administered orally, intraperitoneally, and intravaginally showed no side effect in mice (32).

Curcumin has also shown no toxicity in various clinical trials conducted in humans. The oral dose was standardized for the first time in the phase I clinical trial published in 2001. This study showed that a daily oral intake of 8g is well-tolerated without any side effects (33). Another study was conducted to find out the maximum oral dose which is well-tolerated in humans. This study documented that the daily oral intake can be increased to 12 g without any dose-related side effects (34). Subsequently, there have been numerous phase II and III clinical trials conducted regarding the effective dose of curcumin related to various cancers, inflammatory diseases, Alzheimer's, and other pathologies (35). There are currently over 110 clinical trials under investigation in humans regarding the use of curcumin for various conditions (36). These trials have indicated no serious side effects related to curcumin.

Besides oral administration, curcumin has also been formulated to administer via various routes including intravenous, intraperitoneal, and intravaginal without any side effects (37). Curcumin may also be used topically to treat skin related disorders, including folliculitis, psoriasis, and other skin infections (38,39) without any effect on normal skin cells. Intranasal administration has been a promising route to target the CNS through the blood brain barrier (40,41) and has been shown to cause no side effects.

Curcumin is recognized as safe by the United States Food and Drug Administration (FDA) and has been granted an acceptable daily intake (ADI) level of 0.1-3 mg/kg body weight by the Joint FAO/WHO Expert Committee on Food Additives (3).

3. METHODOLOGY

Most of the studies on curcumin have focused on investigating its anticancer effects and recently

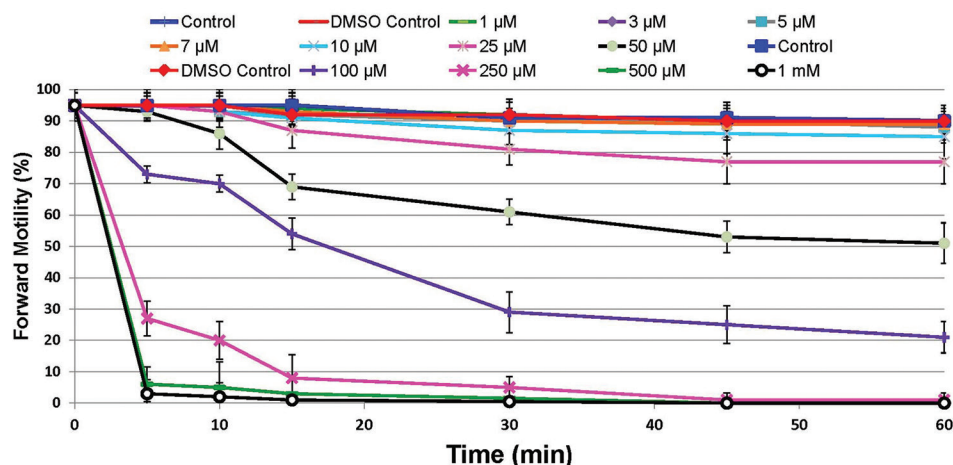


Figure 1. Spermicidal effect of curcumin on human sperm. Effect of various concentrations of curcumin on human sperm forward motility. There was a concentration-dependent decrease in sperm forward motility. Curcumin completely blocked human sperm forward motility at concentrations $\geq 250 \mu\text{M}$ within <5 to 15 min. Values are presented as mean \pm SD of various experiments using sperm from different fertile men. Modified with permission from (49).

anti-Alzheimer effects (42-44). There is a paucity of information, if any, on its utility in the treatment of pathologies related to the female genital tract (FGT). The aim of this review is to examine if curcumin can potentially provide a versatile drug to treat challenges and pathologies uniquely faced by women. The most common challenges faced by women include contraception and vaginal infections. This article will aim at examining the utility of curcumin as a novel, non-steroidal contraceptive which can also combat vaginal infections.

We performed an extensive literature search to examine the available data as related to curcumin and FGT. The Pubmed database (www.pubmed.gov) was searched (1990-2014) using the following Key Words: curcumin and ovarian cancer/cervical cancer/uterine cancer/microbicide/antimicrobial mechanism/antibacterial mechanism/antifungal mechanism/antiviral mechanism/biofilm/sexually transmitted infections/vaginal infections/gonorrhea/chlamydia/syphilis/trichomoniasis/herpes simplex virus/human papillomavirus/human immunodeficiency virus/bacterial vaginosis/yeast infection/endometriosis/menopause/contraception/infertility/sex hormones/ endocrine function. The Pubmed database identified 1220 articles using these Key Words. On the basis of their abstract contents, 154 were selected for full-length articles and analyzed in detail. The publications referenced in these 154 articles were also examined.

4. CURCUMIN AS A CONTRACEPTIVE WITH ANTIMICROBIAL PROPERTIES

4.1. Contraception

The population explosion and increasing rates of unintended pregnancies leading to elective abortions are

major public health issues affecting resources worldwide. The world population has exceeded 7.2. billion and is expected to reach 9.6. billion by 2050 (45). Unintended pregnancies are also a major public health problem faced by sexually active women. The Global Health council estimates that over one-quarter of the world's 1.2. billion pregnancies between 1995-2000 were unwanted (46). Worldwide, there are roughly 80 million unintended pregnancies annually with 45 million of those resulting in an elective abortion (47). This calls for a better method of contraception that is acceptable, effective, non-steroidal, and reversible without any side effects.

Recently, our laboratory examined for the first time ever the potential of curcumin to provide a novel non-steroidal contraceptive. The effect of curcumin was investigated on human sperm function *in vitro*, and on fertility *in vivo* using the mouse model (32). Sperm were collected and incubated with curcumin to examine the effect of motility, capacitation/acrosome reaction, and *in vitro* fertilization (IVF). The effect on *in vivo* fertility using the mouse model was also examined. Incubation of sperm with curcumin caused a concentration-dependent decrease in sperm forward motility, capacitation/acrosome reaction, and IVF. At higher concentrations ($\geq 250 \mu\text{M}$), there was a complete block of sperm motility and function <5 to 15 minutes, depending upon the dose. Administration of curcumin, especially intravaginally, caused a significant reduction in fertility without any side effects. The antifertility effect of curcumin was completely reversible. The effect of various concentrations of curcumin on human sperm forward motility is shown in Figure 1.

In a follow-up study, we tested whether photosensitization of curcumin could reduce the

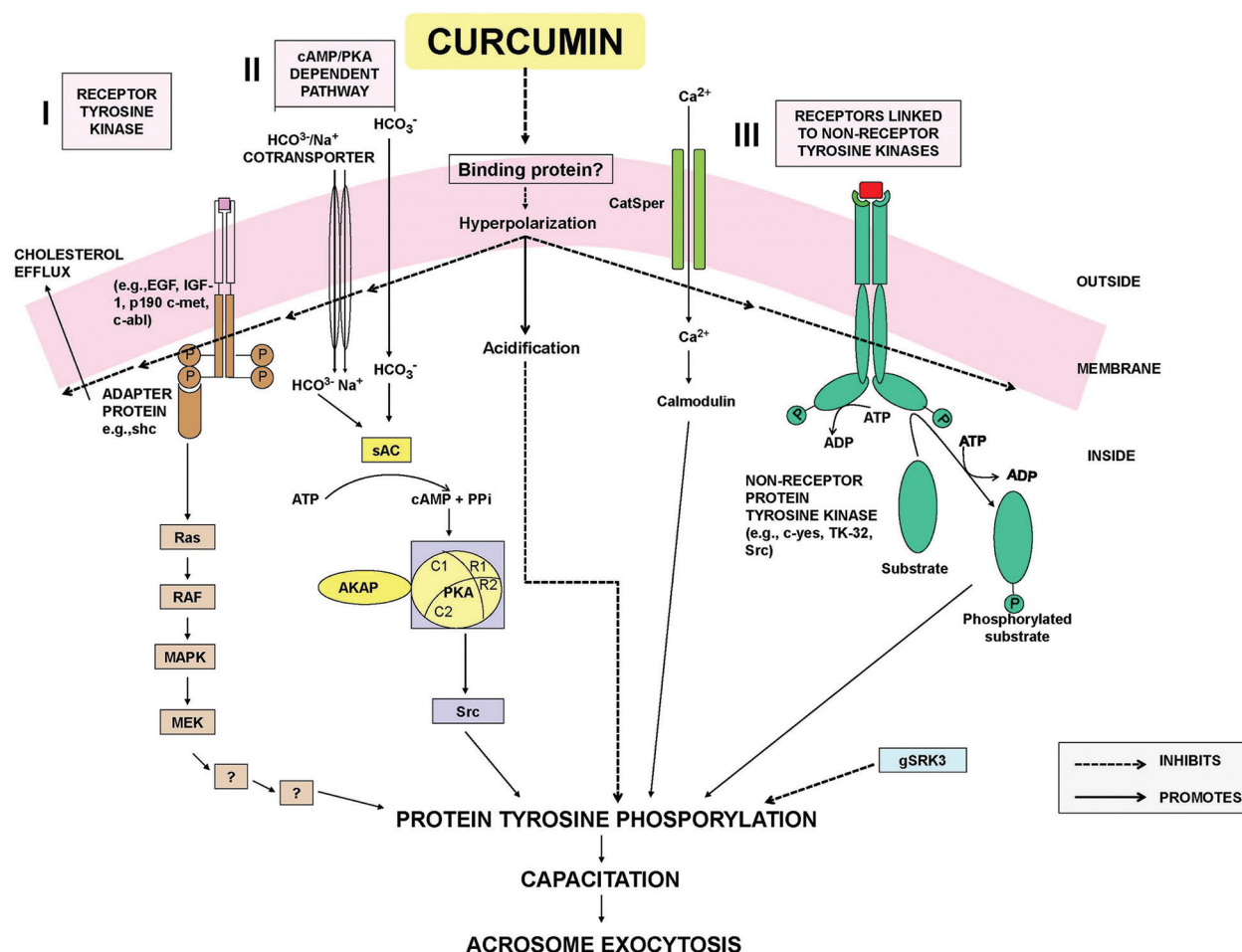


Figure 2. Heuristic model indicating potential targets of curcumin for spermicidal activity. There are several molecular mechanisms involved in sperm motility and capacitation/acrosome reaction. These can be broadly classified into three signal transduction pathways, namely receptor tyrosine kinase (pathway I), cAMP/PKA dependent pathway (pathway II), and non-receptor tyrosine kinase (pathway III). These pathways lead to protein tyrosine phosphorylation of several key proteins. In a recent study, we found that curcumin causes hyperpolarization of the sperm membrane, leading to intracellular acidification (50). This can potentially modulate different pathways/molecules leading to inhibition of sperm motility and function (shown by the dotted (---) line). For details of the various molecules, please see reference 127. Modified with permission from (127).

dose required to completely inhibit sperm motility. Photosensitization at the maximum absorbance (A_{\max}) of a molecule makes it more reactive to the target (48). The photosensitization of curcumin decreased the concentration by 25-fold to completely inhibit sperm forward motility (49). These are exciting findings indeed, demonstrating the spermicidal activity of curcumin which increases drastically after photosensitization.

At this time, the molecular mechanism by which curcumin affects sperm motility and function are not known. In a recent study from our laboratory, the mechanism(s) and signal transduction pathways by which curcumin inhibit sperm motility and function was examined (50). It was found that it causes sperm membrane hyperpolarization resulting in intracellular acidification which could inhibit the sperm forward motility. The exact mechanism/signal transduction pathway(s) is

being delineated. It is hypothesized that these parameters could modulate several molecules and mechanisms, including Ca^{2+} influx and tyrosine phosphorylation, which are vital for sperm motility and function (Figure 2).

There is an urgent need of an acceptable spermicide. At this time, there is no acceptable spermicide available in the market. The most used spermicide, Nonoxonyl-9 (N-9), is a surfactant and causes vaginal irritation including burning and ulceration, which increases the risk of vaginal infections and STIs (51,52). Curcumin can provide an ideal spermicide.

4.2. Vaginal infections

The most common vaginal infections and their infectious agent(s), diagnostic criteria, worldwide prevalence, current treatments methods, and resistance/recurrence data are summarized in Table 1. The vaginal

Table 1. Female genital tract infections (Bacterial/Fungal/Viral)

Infection	Infectious agent (s)	Diagnostic Criteria	Prevalence*	Current Treatment Methods	Resistance/Recurrence*	References
1. <i>Bacterial vaginosis</i>	Increase of specific anaerobes in vaginal flora (i.e. <i>G. vaginalis</i>)	Clinical manifestations (unpleasant discharge), Amsel criteria, gram stain, nucleic acid detection	21.2 million	Antibiotics (oral/ intravaginal metronidazole/ intravaginal clindamycin)	~30-60% recurrence; Metronidazole and clindamycin-resistance is documented	53-58, 62, 65, 72, 111, 112
2. <i>Vulvovaginal candidiasis</i>	Increase of <i>Candida albicans</i> in vaginal flora	Clinical manifestations (itching/ vaginal discharge/soreness/ irritation/vulvar burning/ painful intercourse), positive microscopy	**	Intravaginal azoles (butoconazole/ clotrimazole/ miconazol), oral fluconazole	5% of women get recurrence 4-5 times annually & remaining get 1-4 times annually	53, 70, 72, 113
3. <i>STIs</i>						
Trichomoniasis	<i>Trichomonas vaginalis</i>	Clinical manifestations (vaginal itching/burning/soreness/ dysuria/unpleasant discharge; may be asymptomatic), microscopy, cell culture, nucleic acid detection	3.71 million	Antibiotics (metronidazole/ ornidazole)	~2-5% to metronidazole-resistance	72, 77, 114, 115
Chlamydia	<i>Chlamydia trachomatis</i>	Clinical manifestations (vaginal discharge/painful/burning urination), cell culture	1.57 million	Antibiotics (azithromycin/ doxycycline)	No resistance/recurrence described	77, 114, 116-118
Syphilis	<i>Treponema pallidum</i>	Clinical manifestations (Primary stage: sores; Secondary stage: skin rashes/mucous membrane lesions; Latent/late stage: lack of muscle control/numbness/ blindness/dementia), microscopy, serology test, nucleic acid detection	117,000	Early stages – antibiotics (penicillin/ macrolides/ tetracycline)	Macrolide resistant documented	77, 114, 116, 119-122
Gonorrhea	<i>Neisseria gonorrhoeae</i>	Usually asymptomatic; cell culture, nucleic acid detection	270,000	Antibiotics (cephalosporins)	Resistance to penicillin, tetracycline, fluoroquinolones	77, 98, 114, 116, 117
HPV***	Human papillomavirus	Clinical manifestations (warts; however often asymptomatic), colposcopy, Pap test, nucleic acid detection	79.1 million	Symptomatic treatment of genital warts; Vaccine (Cervarix/Gardasil)	No known antiviral target	36, 116, 123
HSV-2***	Herpes simplex virus 2	Clinical manifestations (genital lesions), viral culture, PCR test, serology test	24.1 million	Antivirals (acyclovir/ famciclovir/ valacyclovir)	Rare resistance in immunocompetent patients	114, 116, 124, 125
HIV/AIDS***	Human immunodeficiency virus	Clinical manifestations (primary infection: flu-like symptoms; AIDS progression: immunocompromisation), serology test, nucleic acid detection	908,000	Combination antiretroviral therapy	~5-15% patients resistant ≥1 antiretroviral drug	114-116, 126

*Prevalence (number of cases at any given time) & Resistance/Recurrence in the United States. **It is estimated that 75% of women will have at least one episode of vulvovaginal candidiasis, or a "yeast infection", in their lifetime. ***Viral STIs which are non-treatable.

infections can be broadly classified into three major categories namely bacterial vaginosis (BV), vulvovaginal candidiasis (VC), and sexually transmitted infections (STIs). Although somewhat distinct, they are not mutually exclusive.

4.2.1. Bacterial vaginosis (BV)

The prevalence of BV among premenopausal women is a significant health issue. One-third of women will develop symptoms of vaginitis sometime during

their lifetime. The most common cause of vaginitis is BV (53,54). The prevalence of BV in US women ranges from 22–50%, but it is difficult to determine the exact prevalence because it is often asymptomatic or self-diagnosed and self-treated (53,54). BV is caused by a complex change in vaginal flora, characterized by a reduction in hydrogen peroxide-producing lactobacilli and an increase in certain anaerobic bacteria, including *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella* spp, *Porphyromonas* spp, *Bacterioides* spp, *Peptostreptococcus* spp, *Mobiluncus* spp, and *Mycoplasma hominis*. (55–58). Clinically, BV is diagnosed when at least three of the four symptoms are present: homogeneous vaginal discharge, vaginal pH greater than 4.5, “fishy” odor on addition of potassium hydroxide to vaginal fluid (positive “whiff test”), and presence of clue cells in microscopy of wet preparation (59). BV is clinically treated using topical or oral metronidazole or clindamycin. However, approximately 30–60 percent of women have a recurrence of symptoms within three months (60,61). The exact reason(s) for recurrence is unclear, but likely reflects vaginal relapse caused by failure to totally eradicate the infectious organisms.

Antibiotic resistance among BV patients is also a serious concern. The treatment of BV with antibiotics is associated with antibiotic resistance, increasing the vaginal reservoir of antibiotic-resistant bacteria (62,63). *Atopobium vaginae*, a major microbe associated with BV, is strongly metronidazole-resistant (64,65).

Our extensive database research did not yield any study which examined the antibacterial effect of curcumin against bacteria involved in BV, other than a recent study conducted in our laboratory, which is discussed below.

The exact antibacterial mechanism(s) of curcumin on bacteria involved in BV has not been studied. However, several studies have examined its antibacterial targets in various non-BV aerobic bacterial species (Figure 3). These targets include peptidoglycan layer, cell organelles, and cell lysis (66). It inhibits the assembly of FtsZ, a prokaryotic homologue of the eukaryotic cytoskeletal protein tubulin, which orchestrates bacterial cell division (67). Its terminal phenyl rings and ketoenol structures bind directly to FtsZ, inhibiting bacterial proliferation (67,68). At this time, curcumin is the only known inhibitor of FtsZ assembly. Curcumin also inhibits biofilm formation, which is one of the major mechanisms by which microbes resist antibiotics and immune surveillance (69).

4.2.2. Vulvovaginal candidiasis (VC)

VC, commonly known as yeast infection, is the second most common cause of vaginal infections and is diagnosed in up to 40% of women with vaginal complaints in the primary care setting (53). Overall prevalence of VC

ranges from 17–40% (53). It is estimated that 75% of women will have at least one yeast infection during their lifetime (70). Additionally, use of the oral contraceptive pill has also been associated with an increased risk of developing VC (71). VC is primarily caused by imbalance in the natural flora of the vagina resulting in an overgrowth of *Candida albicans* and other spp (70). VC is diagnosed by examining the vaginal pH and potassium hydroxide microscopic test (72). VC is clinically treated using topical and oral azole antifungal agents, several of them are also available over-the-counter. However, there is a notable lack of accuracy in self-diagnosis of yeast infections, causing concern over the overuse/abuse of over-the-counter drugs (72). This situation is also a classic paradigm for the emergence of azole-resistant *Candida albicans* and other strains (73).

Several studies show that curcumin is capable of antifungal activity against *Candida albicans*, including our recent study, which is discussed below. It inhibits yeast growth by interacting with several targets (Figure 3). These include generation and accumulation of ROS through accumulation of ergosterol biosynthesis intermediates, resulting in early apoptosis and cell death (74). Curcumin-treated *Candida* cells also have reduced ergosterol levels and significant differences in the level of molecular species of phosphatidylglycerol and sphingolipids, suggesting that there is modification of membrane lipids in response to curcumin treatment (74). It causes cell wall damage in yeast cells, especially by downregulating genes in the cell wall integrity pathway (75). Studies have also shown that it inhibits hyphae development, thus blocking cell proliferation, and inducing ROS leading to cell death (76).

4.2.3. Sexually transmitted infections (STIs)

STIs (viral and non-viral) are a major public health problem in both developed and developing countries. Millions of viral STIs occur annually. These include infections with human immunodeficiency virus (HIV), human papilloma virus (HPV), and herpes simplex virus 2 (HSV-2). Worldwide, an estimated 499 million new cases of non-viral STIs occur each year in people of reproductive age (77). The non-viral STIs are caused by bacterial, mycological, and protozoal agents, and include syphilis, gonorrhea, chlamydia, and trichomoniasis. Besides their obvious effect on the FGT, STIs can also cause infertility, ectopic pregnancy, cervical cancer, and birth abnormalities (78). The use of steroidal contraceptives increases the incidence of STIs (71,79).

There are several studies reporting the anti-viral activity of curcumin against HIV (80–85) and HPV (86–88). We found one study in our literature search which reported antiviral activity of curcumin against HSV-2 (89). Interestingly, curcumin analogues, namely dicaffeoylmethane and rosmarinic acid, inhibit HIV-1 with increased potency (81). There are four major

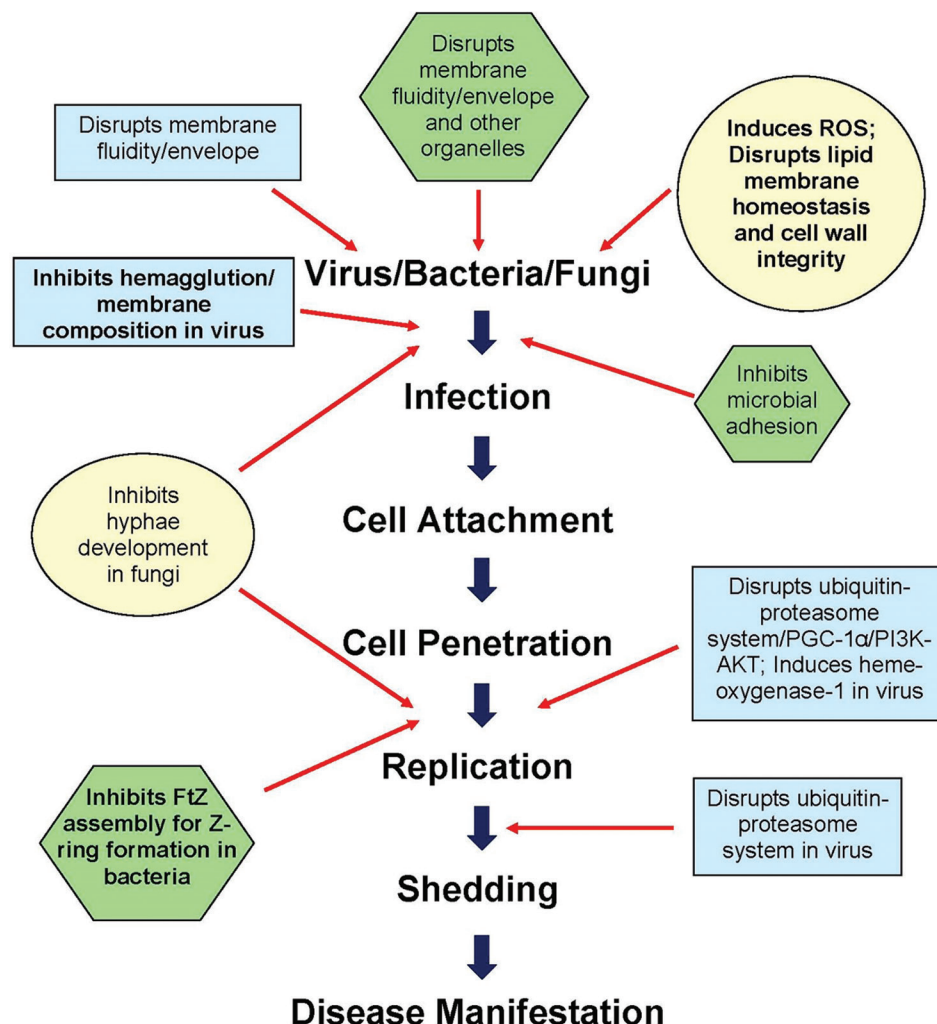


Figure 3. Heuristic model indicating potential targets of curcumin for microbicidal (antibacterial/antifungal/antiviral) activity. Various targets have been postulated for antibacterial, antifungal, and antiviral activities of curcumin. Curcumin can disrupt membrane fluidity/envelope/organelles, cell attachment, cell penetration, replication, and shedding. The specific targets which have been deciphered for antibacterial, antifungal, and antiviral activities are shown in different shaped boxes, respectively. The specific targets which have been deciphered for antibacterial activity (shown by hexagon) are disruption of the membrane fluidity/envelope/other organelles, inhibition of microbial adhesion, and inhibition of FtZ assembly. The specific targets which have been deciphered for antifungal activity (shown by circle) are induction of ROS, disruption of lipid membrane homeostasis/cell wall integrity, and inhibition of hyphae development. The specific targets which have been deciphered for antiviral activity (shown by rectangle) are disruption of membrane fluidity/envelope, induction of heme-oxygenase-1, and inhibition of hemagglutination/membrane composition, and ubiquitin-proteasome system/PGC-1 α /PI3K-AKT.

targets for the antiviral activity of curcumin. The first target is the virus *per se*, the second target is inhibition of virus-cell attachment, the third target is inhibition of viral replication, and the fourth is inhibition of viral shedding (Figure 3). Curcumin affects the virus *per se* by disruption of membrane fluidity and viral envelope structure, as well as inhibition of expression of several genes (90-92). Curcumin inhibits virus-to-cell attachment by affecting hemagglutination of viral membranes. (91) Hemagglutinin is a glycoprotein that is necessary for viruses to bind to cellular membranes. Curcumin disrupts viral replication by inhibiting the ubiquitin-proteasome system (UPS), induction of HO-1, inhibition of inosine-5'-monophosphate (IMP) dehydrogenase, and suppression

of Akt/Akt-sterol regulatory element binding protein 1 (SREBP-1) pathway. (93-95). Disruption of UPS by curcumin also blocks viral shedding.

There have been a few studies on examining the anti-gonorrheal effect of curcumin. Curcumin inhibits adherence of *Neisseria gonorrhea* to cells without causing concomitant cytotoxic effects (96). It could also potentially inhibit gonorrheal infections via vitamin D pathways (97). Its anti-gonorrheal activity is of special interest considering the emergence of *N. gonorrhoeae* as a multidrug-resistant organism. This "superbug" has developed resistance against antimicrobial agents previously used for first-line treatment, and resistance

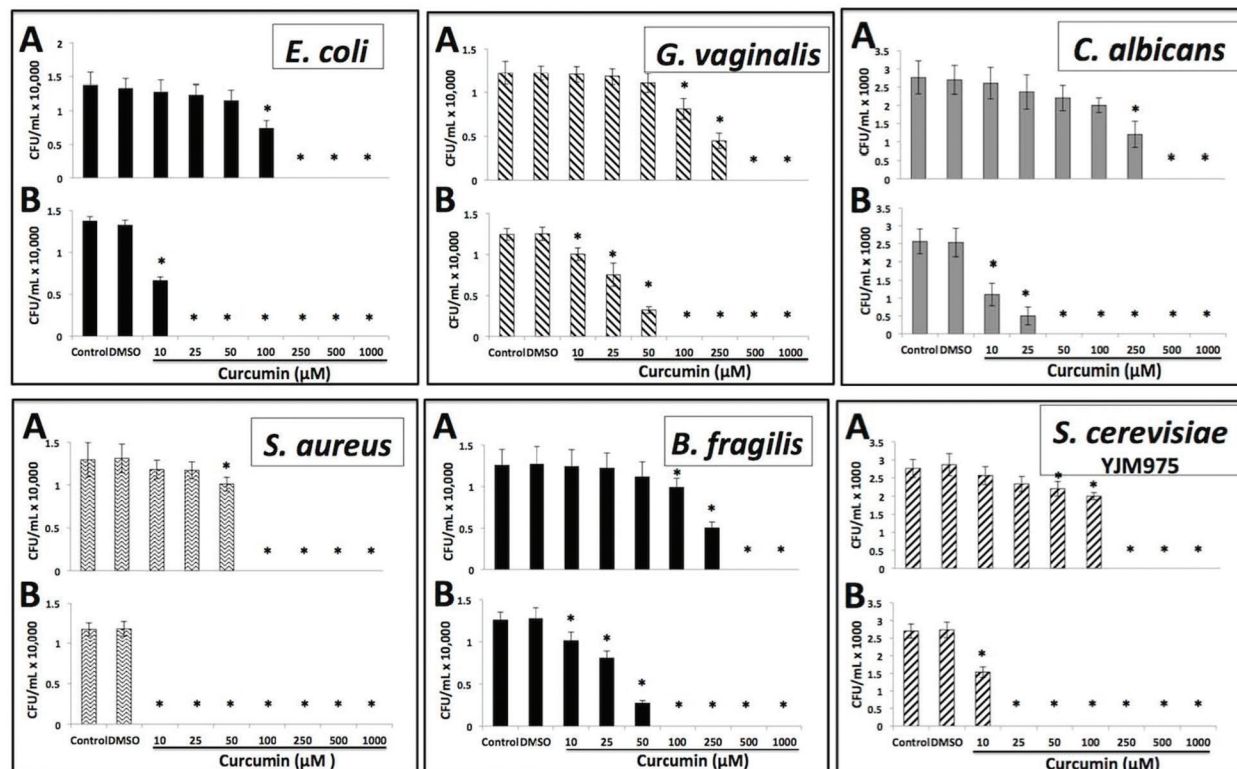


Figure 4. Microbicidal (antibacterial/antifungal) activity of curcumin against microbes implicated in vaginal infections. Effect of various concentrations of un-photosensitized (A panels) and photosensitized (B panels) curcumin on aerobic bacteria, anaerobic bacteria, and yeast species involved in various vaginal infections. Although several species were tested, only two species each of aerobic bacteria (*E. coli* and *S. aureus*), anaerobic bacteria (*G. vaginalis* and *B. fragilis*), and yeast (*C. albicans* and *S. cerevisiae*) are shown here. Curcumin caused a concentration-dependent decrease in microbial growth of all these species, with a complete block at 100-500 µM concentrations. Photosensitization decreased the dose required for complete inhibition by 5- to 10-fold. Values are presented as mean \pm SD of various repeated experiments. Statistically significant differences in microbial growth compared to control are indicated by *. Modified with permission from (49).

against extended-spectrum cephalosporin and ceftriaxone treatment regimen (98).

In a preliminary study, a novel antimicrobial cream, designated as BASANT, was formulated incorporating curcumin and several other herbal medicines. This cream inhibited growth of several classical World Health Organization (WHO) strains and clinical isolates of *Neisseria gonorrhoeae*, including those resistant to several antibiotics. It also demonstrated antimicrobial activity against clinical *Chlamydia trachomatis* isolates. It inhibited growth of *Candida* spp. isolated from women with vulvovaginitis, including isolates which were resistant to azole drugs and amphotericin B. Interestingly, it also exhibited antiviral activity against HIV-1 strains and HPV (99,100).

4.2.4. Recent studies from our laboratory

Our laboratory recently conducted a study to examine the antimicrobial effect of curcumin on several aerobic and anaerobic bacteria, and yeast strains implicated in vaginal infections in women (49). The antibacterial effect of curcumin was examined against

the aerobic bacteria, namely *Alcaligenes faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella choleraesuis*, *Salmonella enteritidis*, and *Yersinia enterocolitica*. Some of these species, namely *E. coli*, *S. aureus*, and *P. aeruginosa* are involved in aerobic vaginitis in women, while vaginal *Salmonella* infections have been linked to miscarriage in women and sexually transmitted enteric disease (101-103). Three aerobic bacteria unrelated to vaginal infections were also included to compare the effect of curcumin on bacteria that cause infections versus those that do not. The effect of curcumin on four anaerobic bacteria species involved in BV, namely *Gardnerella vaginalis*, *Fusobacterium nucleatum*, *Peptostreptococcus anaerobius*, and *Bacteroides fragilis* was examined. The antifungal effect of curcumin against *Candida albicans* and several strains of *Saccharomyces cerevisiae*, including strains from women with vaginal infections was also investigated.

Curcumin blocked growth of all the bacteria (aerobic and anaerobic) and yeast species in a concentration-dependent manner, with a complete block at 100-500 µM concentrations. A higher concentration was

required to block growth of anaerobic bacteria compared to aerobic bacteria. A slightly higher concentration was required to completely block growth of Gram-negative compared to Gram-positive bacteria. Gram-positive bacteria have an outer peptidoglycan layer that is generally permeable, while Gram-negative bacteria have an outer phospholipid membrane with lipopolysaccharide components, which acts as a barrier to molecules.

We investigated whether photosensitization of curcumin could decrease its concentration required to completely inhibit the microbial growth. Indeed, photosensitization decreased the dose required to inhibit growth of both bacteria (aerobic and anaerobic) and yeast by 5- to 10-fold. This is the first study to our knowledge where the effect of curcumin, with and without photosensitization, was examined on bacteria (aerobic and anaerobic) and yeast related to vaginal infections in women. The representative data showing the antimicrobial effect of curcumin on some of these bacteria and yeast, with and without photosensitization, is shown in Figure 4. Photosensitization can be performed at room temperature, and the photosensitized curcumin is stable for some time. Several methods, including use of various media such as Pluronic and nanotechnology, are being investigated in our laboratory to stabilize and increase the half-life of the photosensitized curcumin (104).

It is interesting to note that curcumin has spermicidal and microbicidal activity in the similar dose range.

5. CONCLUSION

Curcumin has a broad range of biological activities, including antioxidant, anti-inflammatory/immunomodulatory, and anticancer properties. Our recent studies, the first of their kind, indicate that curcumin has the potential to provide a novel contraceptive and treatment modality for vaginal infections, including BV, VC, and STIs. Curcumin is a nontoxic molecule classified as safe for human use. Although several clinical trials are going on for many diseases, there are none for the conditions discussed in this review. Our data warrants clinical trials in women for contraception, treatment of vaginal infections, and vaginitis. Curcumin could provide a panacea for FGT pathologies, including gynecologic cancers. Present studies are focused on improving its solubility, bioavailability, and biological activity by deriving curcumin analogs, and development of biodegradable nanoparticles and liposomes (9,105-109). Nanoparticulation enhances half-life, solubility, and absorption of several drugs (3,66,110).

6. ACKNOWLEDGEMENT

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