International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 7 (8): 874-879, 2011
ISSN 1811-7775 / DOI: 10.3923/ijp.2011.874.879

Antibacterial Activities of Curcumin Bioconjugates

[1]Archana Pandey, [1]Ravindra Kumar Gupta, [2]Anudita Bhargava and [1]Babita Agrawal
[1]Department of Chemistry, C.M.P. Degree College (Constituent College of University of Allahabad), Allahabad, India
[2]Department of Microbiology, M.L.N. Medical College, Allahabad, India

Abstract: Curcumin is a wonder molecule as it is used for prevention and cure of multiple diseases such as cancer, diabetes, inflammation, cataract, rheumatoid arthritis, HIV etc., However, it has not been possible so far to assign a definite drug profile because of low bioavailability, fast metabolism, poor adsorption, low solubility and lack of targeted delivery. Several bioconjugate of curcumin with amino acids and nucleotides have been prepared so far to overcome these limitations. In the present study the two new conjugates of curcumin have been synthesized by esterifying its phenolic group functions with nicotinic acid (vitamin B_3) and its isomer picolinic acid viz. 1,7-bis (4-O-nicotinoyl-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione (2) and 1, 7-bis (4-O-picolinoyl-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione (4). These bioconjugate were evaluated for antibacterial activity against medically important gram positive cocci (*Entercoccus faecium*) and gram negative bacilli (*Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*). Antibacterial activity was performed by microdilution broth susceptibility method *in vitro*. Results demonstrated that both bioconjugates possess high antibiotic potential as evidenced by enhanced antibacterial activity in comparison to pure curcumin. On the basis of results it may concluded that lipophilic nature of these conjugates enhances the cellular uptake and may be better option for medicinal and pharmacological applications.

Key words: Curcumin, bioconjugate, nicotinic acid, picolinic acid, antibacterial property

INTRODUCTION

The plant kingdom represents the rich store house of organic compounds which have nutritional as well as medicinal value. Turmeric (*Curcuma longa*) used as dietary spice, has medicinal properties (Srivastava *et al*., 2011) so, it is used as herbal medicine in Ayurveda- the traditional Indian system of medicine. Curcumin, 1, 7-bis (4-hydrxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, the main coloring yellow component is isolated from the rhizomes of turmeric. Curcumin possesses antioxidant (Weber *et al*., 2005) anticancer (Aggarwal and Shishodia, 2006), anti-inflammatory (Chainani-Wu, 2003), antidiabetogenic (Arun and Nalini, 2002; Sivabalan and Anuradha, 2010; Sovia *et al*., 2011), antileshmaniasis (Saleheen *et al*., 2002), Anti-schistosomal (EL-Sherbiny *et al*., 2006) and antimalarial (Reddy *et al*., 2005) activity. It also reduces blood cholesterol (Asai and Miyazawa, 2001; Hasimun *et al*., 2011), suppresses rheumatoid arthritis (Deodhar *et al*., 1980), Alzheimer disease (Yang *et al*., 2005), enhances wound healing (Sidhu *et al*., 1998), protects from liver injuries (Morikawa *et al*., 2002) and cataract formation (Suryanarayana *et al*., 2005). Curcumin is effective to prevent nicotine induced blood cell damage (Banerjee *et al*., 2010).

There are certain limitations which prevent curcumin to use as a drug (Pandey *et al*., 2010) which are as follows:

- It is highly hydrophobic (lipophilic) because of the presence of two free phenolic hydroxyls which make it too polar, restricting its uptake into the cells
- It has low absorption through intestinal gut wall causing its poor systemic bioavailability
- In presence of reductases (Lin *et al*., 2000), it is rapidly metabolized to reduced derivatives like dihydro, tetrahydro and hexahydro curcumin. Recently it has been observed that few endophyte fungi have a potency to generate curcumin analogues by transformation (Prana *et al*., 2010; Simanjuntak *et al*., 2010)

The above limitations can be overcome by attaching curcumin to such ligands which can enhance its solubility, bioavilability and slow down the metabolism. The reactive sites of attachment of ligands to curcumin

Corresponding Author: Archana Pandey, Department of Chemistry, C.M.P. Degree College (Constituent College of University of Allahabad), Allahabad, India Tel: +91-9415045612

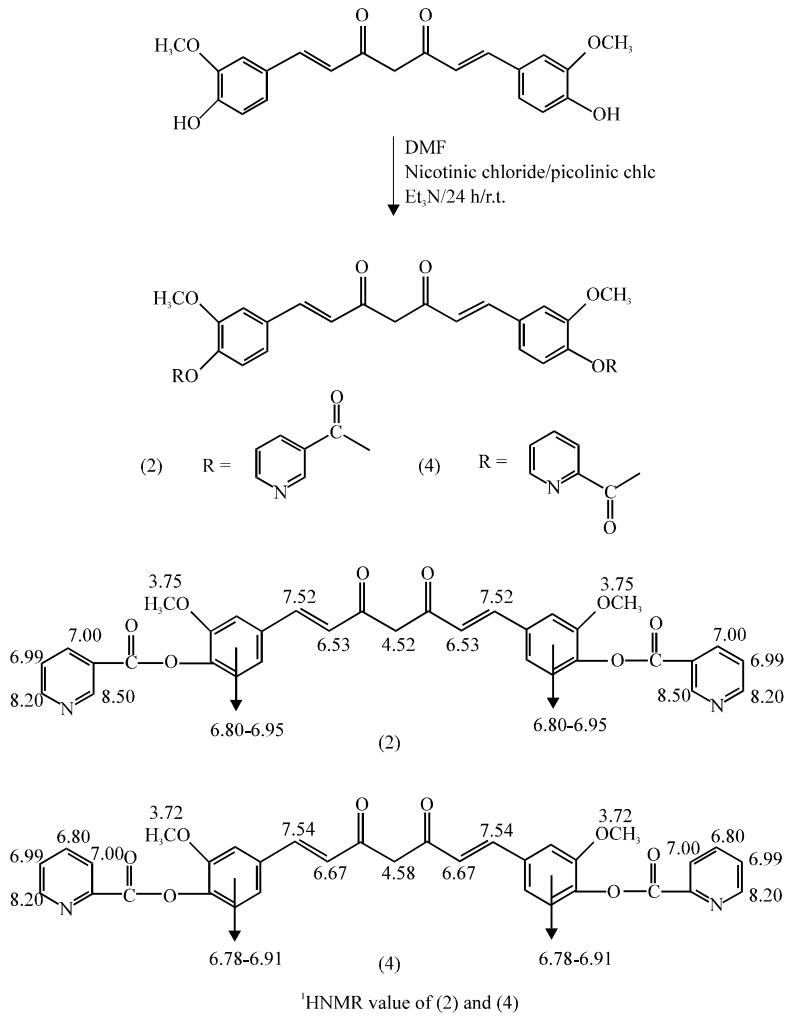

Fig. 1: Synthesis of curcumin bioconjugates

molecule can be either at phenolic hydroxyls, keto or active methylene group. The double bonds are essential for proper conformation of the molecule. The masking of phenolic groups with ligands such as amino acids (Dubey *et al*., 2007) nucleosides (Kumar *et al*., 2001) and peptides (Singh *et al*., 2010) are already reported. Conjugates of curcumin with nicotinic acid (vitamin B_3) and its isomer picolinic acid having biodegradable ester linkage has been synthesized (Fig. 1).

These bioconjugates have been screened for their antibacterial activities. The bacterial resistance is increasing day by day against standard antibiotics so researchers are screening plants (Krishnan *et al*., 2010; Sonibare *et al*., 2011) natural phytochemicals and their derivatives as an option for antibiotics.

Several bacteria are responsible for causing severe infections. *Escherichia coli* cause urinary tract infections and diarrhea (Crichton, 2008). *Pseudomonas aeruginosa* cause primary wound infection, urinary tract infection, and blood stream infection in burn patients (Ekrami and Kalantar, 2007) and respiratory infections (Govan, 2008). *Klebsiella pneumonia* can cause nosocomial infections, urinary tract infections and respiratory tract infections (Crichton, 2008). *Enterococcus faecium* can also cause urinary tract infections and meningitis (Fisher and Phillips, 2009; Ryan and Ray, 2004).

The objective of the present study was to synthesize such conjugates of curcumin which may be lipophilic causing better cellular uptake and show promising antibacterial activity.

MATERIALS AND METHODS

The synthesis, purification and characterization (by spectroscopy) were done in three months duration

i.e., from April-June 2009. Testing of antibacterial activity was performed during April to July 2010.

Curcumin, nicotinic acid, picolinic acid, silica gel G for TLC and silica gel (60-120) for column chromatography were purchased from E. Merck India Ltd. Synthetic grade solvents used were purchased from Qualigens, purified and dried prior to use. UV visible spectra were recorded on Hitachi 220 S double beam spectrophotometer. NMR spectra were recorded using DRX 300 instrument with DMSO as solvent using TMS as internal standard. The Nutrient agar, MacConkey agar, Muellar Hinton agar, Brain Heart Infusion broth and dimethyl sulphoxide (DMSO) were purchased from Himedia Laboratories Pvt. Limited, Mumbai, India.

Nicotinic chloride: Redistilled thionyl chloride (1.09 mL, 0.015 mol) was added to nicotinic acid (1.23 g, 0.01 mol) and refluxed for 30 min. The reaction mixture was evaporated to dryness on rotary evaporator under reduced pressure. Yield = 72% (0.890 g, 6 mmol).

1, 7-bis (4-O-nicotinoyl-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione: Curcumin (100 mg, 0.27 mmol) was taken in dry DMF (dimethyl formamide; 5 mL) and mixed with nicotinic chloride (90 mg≈0.6 mmol). Few drops of triethylamine were added as catalyst. The reaction mixture was stirred overnight at room temperature. The completion of reaction was checked by TLC. Now the reaction mixture is poured into chilled water (10 mL), shaken well and then extracted with DCM (dichloromethane) thrice (5 mL each time). Added Na_2SO_4 (1 g) to the extracted DCM and kept overnight. Filtered the dried reaction mixture, evaporated to dryness and then purified by silica gel column chromatography using DCM/MeOH gradient. Yield 42%, Rf = 0.81 (DCM/MeOH; 9.8 : 0.2). Elemental analysis: Observed- C, 68.49; H, 4.51; N, 4.89% calculated for $C_{33}H_{26}O_8N_2$: C, 68.51; H, 4.49; N, 4.84%. UV λ max (MeOH) = 260 (s), 290, 320 (s) nm. ^{1}HNMR (DMSO-d_6 and D_2O); δ 3.75 (s, 6H, two-OCH_3); 4.52 (s, 2H, C_4 of cur); 6.53 (d, 2H, C_2 and C_6 of cur); 6.80-6.95 (m, 6H, Ar-cur); 6.99 (m, 2H, C_5 of pyridine ring); 7.00 (d, 2H, C_4 of pyridine ring); 7.52 (d, 2H, C_1 and C_7 of cur); 8.20 (d, 2H, C_6 of pyridine ring); 8.50 (s, 2H, C_2 of pyridine ring).

Picolinic chloride: Preparation of picolinic Chloride is similar to that of nicotinic chloride.

1, 7-bis (4-O- picolinoyl-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione: Method of preparation is similar to that of (2).

Rf = 0.80 (DCM/MeOH; 9.8: 0.2). Elemental analysis: Observed-C, 68.50; H, 4.48; N, 4.86% calculated for $C_{33}H_{26}O_8N_2$: C, 68.51; H, 4.49; N, 4.84%. UV λ max (MeOH) = 260 (s), 292, 326nm. ^{1}HNMR (DMSO-d_6 and D_2O); δ 3.72 (s, 6H, two OCH_3); 4.58 (s, 2H, C_4 of cur); 6.67 (d, 2H, C_2 and C_6 of cur); 6.78-6.91 (m, 6H, Ar-cur); 6.80 (m, 2H, C_4 of pyridine ring); 6.99 (m, 2H, C_5 of pyridine ring); 7.00 (d, 2H, C_3 of pyridine ring); 7.54 (d, 2H, C_1 and C_7 of cur); 8.20 (d, 2H, C_6 of pyridine ring).

Antibacterial assay

Minimum inhibitory concentration (MIC): The antibacterial activity of curcumin and its synthetic bioconjugates (2) and (4) were evaluated by microdilution broth susceptibility method against gram positive and gram negative bacteria. The bacterial strains used for testing antibacterial activity were *Klebsiella pneumoniae* (clinical isolates), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and *Entercoccus faecium* (ATCC 33186).

The antibacterial activity of curcumin bioconjugates (2) and (4) were compared with that of curcumin. Stock solution of test agents (1 mg mL^{-1} concentration) was made in DMSO (dimethyl sulphoxide) to ensure complete solubilization (Liang *et al*., 2008). Sterile BHI broth (500 µL) was taken in a set of five sterile test tubes for one bacteria and one compound. To the first tube of each set 500 µL of 1 mg mL^{-1} of stock solution was added and then doubly diluted to the effective final concentrations of 500, 250, 125, 62.5 and 31.2 µg mL^{-1} in the subsequent test tubes. The fresh cultures of aforementioned bacterial strains were prepared and a standardized bacterial suspension of 0.5 Mc Farland turbidity was prepared and 100 µL of this was added to each tube. Now each five tube has a final volume of 600 µL with effective compound concentrations of 300, 150, 75, 37.5 and 18.75 µg, respectively. Suitable solvent control DMSO (to check sterility), DMSO+bioconjugate+BHI, without bacteria (to checks sterility) and positive growth control (DMSO + BHI + bacteria, without bioconjugate - to check bacterial growth) were also run simultaneously (Talaro and Talaro, 2002). The tubes bearing different concentration of curcumin bioconjugates and three above mentioned control tubes were incubated at 37°C for 24 h. After incubation, antibacterial activity of curcumin bioconjugates in the test tube was detected by lack of turbidity which indicates the inhibition of bacterial growth (Talaro and Talaro, 2002; Forbes *et al*., 2007). The concentration in the test tube with highest dilution showing no turbidity was recorded as MIC. Each test was performed in triplicate and the result of at least two repetitions was reported as MIC of the bioconjugates against that particular bacterial strains.

Minimum bactericidal concentration (MBC): The solution of tube with no turbidity and a solution of tube with one higher concentration were sub-cultured on suitable culture media (*Klebsiella pneumonia* and *Escherichia coli* on MacConky agar, *Pseudomonas aeruginosa* on nutrient agar and *Enterococcus faecium* on blood agar) and incubated overnight at 37°C. The highest dilution showing no growth on subculture was recorded as MBC.

RESULTS AND DISCUSSION

In order to prepare curcumin bioconjugates, nicotinic acid is selected as:

- It is a constituent of vitamin B-complex and it can be taken orally like curcumin.
- It contains hetrocyclic nucleus which is generally found in antibacterial compounds.

So, the hypothesis was that the curcumin bioconjugate with nicotinic acid may show enhanced antibacterial activity as it is evident from results of this experiment, shown in Table 1. Picolinic acid is the isomer of nicotinic acid so it is also used as ligand. Curcumin is linked with these ligands by ester bond which may get hydrolyzed by esterase enzymes present in the cells and these results in the increased effective concentration causing enhanced antibacterial activity.

The systemic bioavailability of curcumin is due to the fast metabolism as it is biotransformed to dihydro, tetrahydro and hexahydro-curcumin in presence of reductases, but the curcumin bioconjugates can not be recognized by the above enzymes (as enzymes are specific in reactions) so their biotransformation may be prevented. Also the lipophilicity of curcumin bioconjugates is supposed to be more than the curcumin itself so their cellular uptake may be better.

The antibacterial activity of curcumin bioconjugates (2) and (4) in comparison to curcumin was investigated *in vitro* against *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Entercoccus faecium* (Table 1). The curcumin and its bioconjugates (2) and (4) exhibited antibacterial activity against all the four tested microorganisms. The antibacterial activity assay was done to determine the MIC. The bioconjugate (2) and (4) have shown remarkable antibacterial activity with MIC 0.26 μmol against gram positive cocci (*Enterococcus faecium*) as well as against gram negative bacilli (*Klebsiella pneumoniae, Eschirichia coli* and *Pseudomonas aeruginosa*). The MBC values of all the three samples are higher than that of MIC against all the four mentioned bacteria. It is expected also because the concentration required to kill a microorganism would be definitely higher than the concentration required inhibiting its growth. The MBC value of compound (2) and (4) is found to be 0.52 μmol against *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, but in case of *Escherichia coli* compound (2) and in case of *Entercoccus faecium* compound (4) shows >0.52 μmol. On the other hand the MBC value of pure curcumin is 0.82 μmol against *Klebsiella pneumoniae* and *Escherichia coli* and >0.82 μmol for *Entercoccus faecium*. These MBC value are higher than the synthesized bioconjugates. However, it is found to be 0.41 μmol in case of *Pseudomonas aeruginosa*.

Table 1: Antibacterial activity, MIC and MBC of curcumin bioconjugate (2) and (4) in comparison with curcumin

Bacteria	Compound	Antibacterial activity	MIC (μmol)	MBC(μmol)
Klebsiella pneumoniae	Curcumin	+	0.82	0.82
(clinical isolates)	(2)	+	0.26	0.52
	(4)	+	0.26	0.52
Eschirichia coli	Curcumin	+	0.82	0.82
(ATCC 25922)	(2)	+	0.26	>0.52
	(4)	+	0.26	0.52
Pseudomonas	Curcumin	+	0.20	0.41
aeruginosa	(2)	+	0.26	0.52
(ATCC 27853)	(4)	+	0.26	0.52
Entercoccus faecium	Curcumin	+	0.20	>0.82
(ATCC 33186)	(2)	+	0.26	0.52
	(4)	+	0.26	>0.52

(2): 1, 7-bis (4-O-nicotinoyl-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione
(4): 1, 7-bis (4-O-picolinoyl-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione

The MIC of curcumin bioconjugates (2) and (4) for *Klebsiella pneumonia* and *Eschirichia coli* was found to be lower (0.26 μmol) than that of curcumin (0.82 μmol). The antibacterial activity of bioconjugates (2) and (4) was found to be 3.15 times higher than that of curcumin itself against *Klebsiella pneumoniae* and *Escherichia coli*. Several other conjugates of curcumin (Kumar *et al*., 2001, 2000; Mishra *et al*., 2005; Tajbakhsh *et al*., 2008; Singh *et al*., 2010; Kapoor *et al*., 2006, 2007) also showed more antibacterial activity. In case of *Pseudomonas aeruginosa* and *Entercoccus faecium*, the MIC of curcumin was found to be 0.20 μmol which shows that the activity of bioconjugates (2) and (4) will be 0.76 times less than that of curcumin.

The reason for higher MIC of curcumin bioconjugates against *Pseudomonas aeruginosa* and *Entercoccus faecium* needs further evaluation. Bacterial factors may be playing a pivotal role here since these two bacteria are different in many ways from *Klebsiella pneumoniae* and *Escherichia coli*, both of which belong to same family enterobacteriaceae.

Entercoccus faecium is a gram positive cocci and has a very different cell wall structure with a very high concentration of peptidoglycan and teichoic acid in their cell wall. *Pseudomonas aeruginosa* is however, gram negative having the same cell wall composition as *Klebsiella pneumoniae* or *Escherichia coli*, but its biochemical nature is very different. It is a non-fermenter and a strict aerobe as compared to other two gram negative bacteria which ferment sugar and are facultative anaerobe. May be these differences are responsible for their different activity against curcumin and its bioconjugates. These bioconjugates can be subjected for clinical trials. If encouraging results are found, these conjugates may be used as antibiotics.

CONCLUSION

In the present investigation the bioconjugates of curcumin (2) and (4) have shown remarkable antibacterial activity. The bioconjugates (2) and (4) showed more antibacterial activity than curcumin against *Klebsiella pneumonia* and *Eschirichia coli* while these conjugates are less active than curcumin against *Pseudomonas aeruginosa* and *Entercoccus faecium.*

ACKNOWLEDGMENT

The authors are thank full to University Grant Commission, New Delhi, India for financial assistance and the Chemistry Department, CMP Degree College (Constituent College of University of Allahabad) for providing necessary facilities.

REFERENCES

Aggarwal, B.B. and S. Shishodia, 2006. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem. Pharmacol., 71: 1397-1421.

Arun, N. and N. Nalini, 2002. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant Foods Hum. Nutr., 57: 41-52.

Asai, A. and T. Miyazawa, 2001. Dietary curcuminodoids prevent high-fat diet-induced lipid accumulation in rat liver and epididymal adipose tissue. J. Nutr., 131: 2932-2935.

Banerjee, S., G. Bandyopadhyaya, K. Chattopadhyay and B.D. Chattopadhyay, 2010. Amelioration of nicotine-induced damage of blood cells in protein malnourished female rats by curcumin. Int. J. Pharmacol., 6: 444-455.

Chainani-Wu, N., 2003. Safety and anti-inflammatory activity of curcumin: A component of tumeric (*Curcuma longa*). J. Altern. Complement Med., 9: 161-168.

Crichton, P.B., 2008. Enterobacteriaceae: Escherichia, Klebsiella, Proteus and other genera. In: Mackie and McCartney Practical Medical Microbiology, Collee, J.G., B.P. Marmion, A.G. Fraser and A. Simmons (Eds.). 14th Edn., Elsevier, New Delhi, India, ISBN: 978-81-312-0393-4, pp: 361-384.

Deodhar, S.D., R. Sethi and R.C. Srimal, 1980. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). Indian J. Med. Res., 71: 632-634.

Dubey, S.K., V. Dwivedi and K. Misra, 2007. Novel method for preparation of monoesters of symmetric diphenolic compounds like curcumin (1,7-Bis (4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3, 5-dione) via solid-phase synthesis. Synth. Commun., 37: 4265-4271.

EL-Sherbiny, M., M.M. Abdel-Aziz, K.A. Elbakry, E.A. Toson and A.T. Abbas, 2006. Schistosomicidal effect of curcumin. Trends Applied Sci. Res., 1: 627-633.

Ekrami, A. and E. Kalantar, 2007. Bacterial infections in burn patients at a burn hospital in Iran. Ind. J. Med. Res., 126: 541-544.

Fisher, K. and C. Phillips, 2009. The ecology, epidemiology and virulence of Enterococcus. Microbiology, 155: 1479-1757.

Forbes, B., D. Sahm and A. Weissefld, 2007. Laboratory Methods and Strategies for Antimicrobial Susceptibility Testing. In: Bailey and Scotts Diagnostic Microbiology, Forbes, B., D. Sahm and A. Weissefld (Eds.). 12th Edn., Mosbey, St. Louis, ISBN-13: 978 0 323 03065 6, pp: 187-214.

Govan, J.R.W., 2008. Pseudomonas, Stenotrophomonas, Burkholderia. In: Mackie and McCartney Practical Medical Microbiology, Collee, J.G., B.P. Marmion, A.G. Fraser and A. Simmons (Eds.). 14th Edn. Elsevier, New Delhi, India, ISBN: 978-81-312-0393-4, pp: 413-424.

Hasimun, P., E.Y. Sukandar, I.K. Adnyana and D.H. Tjahjono, 2011. Synergistic effect of curcuminoid and s-methyl cysteine in regulation of cholesterol homeostasis. Int. J. Pharmacol., 7: 268-272.

Kapoor, N., A. Sharma, V. Dwivedi, A. Kumar, U. Pati and K. Mishra, 2006. Telomerase targated anticancer bioactive prodrug by antisense based approach. Cancer Lett., 248: 245-250.

Kapoor, N., U. Narain, V. Dwivedi and K. Misra, 2007. Bioactive conjugates of curcumin having ester, peptide, thiol and disulfide links. J. Sci. Ind. Res., 66: 647-650.

Krishnan, N., S. Ramanathan, S. Sasidharan, V. Murugaiyah and S.M. Mansor, 2010. Antimicrobial activity evaluation of *Cassia spectabilis* leaf extracts. Int. J. Pharmacol., 6: 510-514.

Kumar, S., K.K. Dubey, S. Tripathi, M. Fujii and K. Mishra, 2000. Design and synthesis of curcumin bioconjugates to improve systemic delivery. Nucleic Acids Symp. Ser., 44: 75-76.

Kumar, S., U. Narain, S. Tripathi and K. Misra, 2001. Syntheses of curcumin bioconjugates and study of their antibacterial activities against α-actamase-producing microorganisms. Bioconjugate Chem., 12: 464-469.

Liang, G., S. Yang, L. Jiang, Y. Zhao and L. Shao *et al*., 2008. Synthesis and anti-bacterial properties of mono-carbonyl analogues of curcumin. Chem. Pharm. Bull., 56: 162-167.

Lin, J.K., N.H. Pan and S.Y. Lin-Shiau, 2000. Recent studies on the biofunctions and biotransformation of curcumin. Biofactors, 13: 153-158.

Mishra, S., U. Narain, R. Mishra and K. Mishra, 2005. Design, development and synthesis of mixed bioconjugates of piperic acid-glycine, curcumin-glycine/alanine- and curcumin-glycine-piperic acid and their antibacterial and antifungal properties. Bioorg. Med. Chem., 13: 1477-1484.

Morikawa, T., H. Matsuda, K. Ninomiya and M. Yoshikawa, 2002. Medicinal foodstuffs. XXIX. Potent protective effects of sesquiterpenes and curcumin from zedoariae rhizoma on liver injury induced by D-alactosamine/lipopolysaccharide or tumor necrosis factor-α. Biol. Pharm. Bull., 25: 627-631.

Pandey, A., V. Dwivedi and K. Misra, 2010. Drug Sensitivity of Curcumin Analogues and Bioconjugates. In: Comprehensive Bioactive Natural Product. Volume 7: Structural Modification and Drug Development, Gupta, V.K., S.C. Taneja and B.D. Gupta (Eds.). Studium Press, USA., pp: 267-298.

Prana, T.K., J. Srikandace, E. Sumitro and D. Wulandari, 2010. The potency of endophytic fungi of turmeric (*Curcuma longa* L.) in biotransformation of curcumin compounds in various media. Res. J. Microbiol., 5: 1189-1198.

Reddy, R.C., P.G. Vatsala V.G. Keshamouni, G. Padmanaban and P.N. Rangarajan, 2005. Curcumin for malaria therapy. Biochem. Biophys. Res. Commun., 326: 472-474..

Ryan, K.J. and C.G. Ray, 2004. Sherris Medical Microbiology. 4th Edn., McGraw Hill, New USA., ISBN: 0-8385-8529-9.

Saleheen, D., S.A. Ali, K. Ashfaq, A.A. Siddiqui, A. Agha and M.M. Yasinzai, 2002. Latent activity of curcumin against lishmaniasis *in vitro*. Biol. Pharm. Bull., 25: 386-389.

Sidhu, G.S., A.K. Singh, D. Thaloor, K.K. Banaudha, G.K. Patnaik, R.C. Srimal and R.K. Maheshwari, 1998. Enhancement of wound healing by curcumin in animals. Wound Repair Regen, 6: 167-177.

Simanjuntak, P., T.K. Prana, D. Wulandari, A. Dharmawan, E. Sumitro and M.R. Hendriyanto, 2010. Chemical studies on a curcumin analogue produced by endophytic fungal transformation. Asian J. Applied Sci., 3: 60-66.

Singh, R.K., D. Rai, D. Yadav, A. Bhargava, J. Balzarini and E. De Clercq, 2010. Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid. Eur. J. Med. Chem., 45: 1078-1086.

Sivabalan, S. and C.V. Anuradha, 2010. A comparative study on the antioxidant and glucose-lowering effects of curcumin and bisdemethoxycurcumin analog through *in vitro* assays. Int. J. Pharmacol., 6: 664-669.

Sonibare, M.A., T.O. Lawal and O.O. Ayodeji, 2011. Antimicrobial evaluation of plants commonly used in the management of psychosis opportunistic infections. Int. J. Pharmacol., 7: 492-497.

Sovia, E., E.Y. Sukandar, J.I. Sigit and L.D.N. Sasongko, 2011. Improvement of pancreatic langerhans islets by curcuminoid, S-methyl cysteine and its combination: An immunohistochemistry analysis. Int. J. Pharmacol., 7: 410-414.

Srivastava, R., A. Pandey and R.K. Gupta, 2011. Curcumin-the yellow magic. Asian J. Applied Sci., 4: 343-354.

Suryanarayana, P., M. Saraswat, T. Mrudula, T.P. Krishna, K. Krishnaswamy and G.B. Reddy, 2005. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. Invest. Ophthalmol. Vis. Sci., 46: 2092-2099.

Tajbakhsh, S., K. Mohammadi, I. Deilami, K. Zandi, M. Fouladvand, E. Ramedani and G. Asayesh, 2008. Antibacterial activity of indium curcumin and indium diacetylcurcumin. Afr. J. Biotechnol., 7: 3832-3835.

Talaro, K. P., and A. Talaro, 2002. Drugs, Microbes, Host: The Elements of Chemotherapy. In: Foundation in Microbiology, Talaro, K.P. and A. Talaro (Eds.). 4th Edn. McGraw Hill, New York, USA., pp: 348-379.

Weber, W.N., L.A. Hunsaker, S.F. Abcouwer, L.M. Deck and J.D.L. Vander, 2005. Antioxidant activities of curcumin and related enones. Bioorg. Med. Chem., 13: 3811-3820.

Yang, F., G.P. Lim, A.N. Begum, O.J. Ubeda and M.R. Simmons *et al*., 2005. Curcumin inhibits formation of amyloid beta oligomers and fibrils, bind plaques and reduce amyloid *in vivo*. J. Biol. Chem., 280: 5892-5901.