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MODULATION OF CURCUMIN AND ITS DERIVATIVES AS AN ANTITUMOR AGENT

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ABSTRACT

It has been proven that curcumin has an anti-tumor action against many types of cancer. The determined pathway by which curcumin acts as an antitumor agent is not fully understood. This review focuses on the pathways that could be possessed by curcumin as an antitumor agent, especially STAT-JNK, Ras/Raf/MAP kinase (ERKs JNK, and p38-MAPKs), TNF, and MMP-2,9 and how they are cross-linked. For this systemic search, we established an investigative approach to classify related literature (PRISMA framework). This approach was fitted to four databases: Scopus, Web of Sciences, Direct, and Google Scholar. The search words used are "curcumin", "Raf/MAP Kinase", "ERKs"," JNK", "P38-MAPKs", "STAT", and "MMP". All searches covered from database launch until 2021 included articles and reviews published in English only. The inclusive systematic review of this research showed that curcumin treatment affected multiple signaling pathways activated in cancer progression.

KEYWORDS: curcumin; STAT-JNK; Ras/Raf/MAP kinase; ERKs; TNF; MMP-2,9.

INTRODUCTION

Cancer is a malignant growth and uncontrolled division of cells.

Using chemotherapy and radiation therapy has various side effects that limit their use, hence the need for finding a natural product of low toxicity is increased markedly. There is an increase in cancer cases with limited treatment opportunities and low survival ratios. (Roxburgh & Jeffry Evans, 2008)(Zhong et al., 2019)(O'Grady & Lawless, 2015)

Curcumin (diferuloylmethane) or 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione], the main constituent of turmeric (a yellow compound isolated from the plant Curcuma longa L. Over) has biological and pharmacological actions including anti-mutagenic, anti-carcinogenic (Aggarwal & Harikumar, 2009), anti-bacterial (Tham et al., 2010), antioxidant (Properties, 2006), anti-malarial, anti-angiogenic, chemo-preventive, immune-modulatory (Tham et al., 2010), and anti-inflammatory (Tham et al., 2015), Cardiovascular, Metabolic, and Autoimmune Diseases. (Aggarwal & Harikumar, 2009)

It controls various cellular signaling pathways, gene expression, and enzyme activity. It has impact on pro-inflammatory cytokines like IL-6; Interleukin (IL)-1, prostaglandin, protein kinases, inducible enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), transcription factors such as NF-κB, STAT-3 and AP-1, p-38 and mitogen-activated protein kinase (MAPK), interleukin (IL)-10, and tumor necrosis factor (TNF)-α. (Tham et al., 2021)

Curcumin is safe (up to 12 g/day dose) and effective agent, it is well tolerated with limited toxicity, but it has poor bioavailability due to first-pass effect conjugation after oral administration, poor absorption and rapid metabolism and elimination.

The poor bioavailability of curcumin could be overcome by using of liposomes that can carry hydrophilic and hydrophobic molecules, interfering glucuronidation by using of hepatic and intestinal glucuronidation inhibitors like piperine, nanoparticles encapsulation, the use of structural curcumin analogs of like EF-24 that have rapid absorption, the use of phospholipid complexes, chelation with metal, phospholipid complex, isomerization. (Santosh k. Sandur, 2007) And synthesizing analogs.

2,6-bis-(4-hydroxy-3-methoxybenzylidine) cyclohexanone (BHMC) was synthesized as an analog of curcumin (figure 1: B), in which ß-diketone part of

curcumin was transformed into a conjugated double bond whereas phenolic OH group was kept for its antioxidant activity.(figure 1: A). (Alwi et al., 2019)

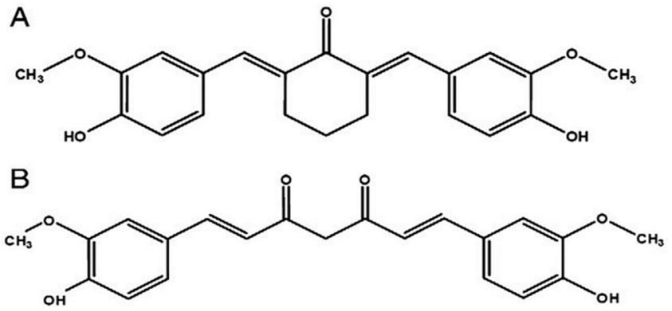


Figure 1: Chemical structures of curcumin (B) and BHMC (A).

Harun (2018) revealed that BHMC prevented cancer invasion, the precursor step for metastasis of breast cancer, by inhibiting invadopodia formation and its related proteins like MMP-9.

Nanocurcumin prevents stimulation of the transcription factor NF-κB and decreases concentrations of pro-inflammatory cytokines. Curcumin can suppress the inflammation process by inhibiting STAT 3, the proinflammatory cytokine IL-6 mediator. (Aggarwal & Harikumar, 2009) (Garcea et al., 2005)

Dysregulation of multiple gene products causes most of diseases like TNF, COX-2 inhibitor, epidermal growth factor receptor, and VEGF. Dysregulated inflammation causes most chronic illnesses including cancer.

Curcumin down-regulates the expression of TNF, IL-6 protein, COX-2, adhesion molecules, NF-κB, VEGF, MMP-9, STAT, PI3K-AKt, IL-8, c-reactive protein (CRP), TNF and other chemokines.

Curcumin is a potent antitumor agent against blood, breast, brain, gastrointestinal system, liver, multiple myeloma, pancreas, prostate, colon, ovary, head and neck, skin, adenomatous polyposis, advanced pancreatic, and advanced colon cancer.

Table -1 illustrates the information extracted from studies done using curcumin and its derivatives.

DISCUSSION

JAK/STAT, Raf/MEK/ERK, and PI3K/Akt pathways: The activation of surface receptors leads to activation of JAK / STAT that affects the gene expression nucleus; this leads to activation of PI3K that activates Ras/Raf/MEK/ERK that also affects the gene expression nucleus which activate Akt that activates NF-kB that affects gene expression nucleus. (12) JAK (Janus family of tyrosine kinases) and STAT (signal transducers and activators of transcription) transfer signals from receptor to nucleus. Cytokine receptors activate JAKs that stimulate STAT transcription factor activity. It is intricate in tumorigenesis, cell cycle, migration, proliferation, and apoptosis. It is dysregulated in many cancer types, and unphosphorylated STAT acts as a tumor suppressor when interacting with a specific protein. (Thomas et al., 2015)

ERK (extracellular signal-regulated kinase) or MAPK (mitogen activated protein kinase) family of genes are substrates of MEK. ERK transmits signals from cell surface receptors to transcription factors in the nucleus as growth factors, mitogens, and cytokines. PI3K/Akt and JAK/STAT pathway cross talks with Raf/MEK/ERK via Ras proteins activation. Raf is part of p53 and NF-kB transcription factors activation, cell cycle progression, nonenzymatic functions, docking protein, and apoptosis prevention. MEK proteins are targets of Raf. (Dai et al., 2009)

Phosphorylation and glutathionylation activate the members of MAPK signaling pathways like ERK, EGF receptor, VEGF and RAS phosphorylation. The activation of lead to activation of Ral1, RhoA, Rac1 and TNF family receptors. Rho/Rac proteins are GTPase family members of Ras superfamily of GTP hydrolases. (Szczepanowska, 2009) These proteins are classified into six subfamilies: Rho (ROCK: Rho associated kinase), Rac, Cdc42, Rnd, RhoBTB and RhoT/Miro. They have a role in cytoskeletal events control, and other cellular functions like cell polarity, transcriptional dynamics, vesicular trafficking, and cell cycle. RhoA is the first member identified by Ras - related genes with conventional cloning techniques. RhoA is phosphorylated by ERK (extracellular signal-related kinase) in response to EGF stimulation, which up-regulates Rho A activity. Rho A has a role in the formation of stress fibers, cytokinesis and cell motility. ERK (Epidermal response factor) interacts with RhoA. EGF stimulation enhanced the activation of the endogenous RhoA.

Rho GTPases play roles in regulating cell proliferation, size, polarity, apoptosis, membrane trafficking, motility, adhesion, post-transcriptional regulation and phosphorylation. (Tong et al., 2016)

p21-activated kinases (PAKs) are serine/threonine protein kinases interacting with small GTPases (Ras, Rho, Rac and Cdc42) implicated in the cytoskeletal organization, migration, invasion, cell survival, and proliferation, by phosphorylation and inactivation of a pro-apoptotic protein—BAD- BCL2 antagonist of cell death—inhibiting the proapoptotic effects of BAD. Gene mutation regulating these processes transforms

a normal cell into a cancer cell. PAKs act as signal transducers in most cancer signaling pathways, including Ras, Bad, Raf, NF-kB, Akt, and p53. PAKs are over-expressed, hyper-activated, or amplified in human cancer but not mutated. (Yang, 2016)

Mitogens activate microtubule-associated protein that is phosphorylated by ERKs. The JNK and p38 kinase pathways are called stress-activated protein kinases. MAP/ERK Kinase activates Ras/Raf family via phosphorylation. Tumor necrosis factor (TNF) and FAS receptors activate the JNK signaling pathway. TNF family activates the p38 pathway via the activation of cdc42, while growth factor receptors activate this pathway via RAS and Rac1 activation. JNK pathway activates p38 pathway. Growth factor removal can activate p38 pathway. It up-regulates the matrix metalloproteinases -regulates matrix degradation, and VEGF -tumor survival and angiogenesis inducer. Transcription factors like p53 are mainly phosphorylated -activated- by p38 MAPK.

According to some studies, CDK activity inhibits apoptosis and promotes cell cycle by reducing retinoblastoma (Rb) protein phosphorylation, or it may be related to temperature. Cdks act in apoptosis by direct phosphorylation of the proapoptotic protein. Inhibition of the CDK2 cell cycle protein kinase complex protects the cell against apoptosis. Cell cycle arrest status is regulated by the phosphorylation and dephosphorylation states of CDKs and other regulatory factors. (Wang et al., 2015), P16 is a CDK inhibitor. TQ decreases cyclinD1 and cyclin B1 levels and increases P16 and P53 (tumor suppressor protein) expression. (49) Cdks migh t function in vitro. Cyclin E has a role in radiation-induced apoptosis. (18) An associated with cyclins is a step required for CDKs to positively regulate cell cycle progression. Several reports have shown the correlation between the activation of CDKs and apoptosis. Inhibition of CDK2 activity can block apoptosis activity and increase CDK2 kinase activity that integrates with two different signal transduction pathways. Apoptosis that uses cell cycle proteins does not need a specific phase of the cell cycle; apoptosis happens in mitochondria. Inhibitors of CDKs like P21 and P27 that inhibit cyclin-dependent kinases may block apoptosis. Proteolytic synthesis regulates the cell cycle. It is a sequence of cyclin proteins that activates cdks. Each cyclin binds to a specific cdk catalytic subunit. Cyclin D is required for interphase S and G1, whereas cyclins A and B are required for the G2/M phase.

MMP-2,9

MMP-9 (matrix metalloproteinase 9) expression with the collaboration of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) monitor cell spreading and migration involved in the repair process. It stimulates angiogenesis, metastasis, invasion, survival, and growth of malignant cells. MMP-9 with collagen IV stored in the epithelial actin-dependent pathway and got active in the extracellular matrix (ECM). (Legrand et al., 1999) In most types of cancer, MMP-9 is found to be hyperexcited.

Guo (2015) illustrated that MMP-9 is an ovarian cancer-associated gene. Inhibition of MMP-9 stimulates cell apoptosis in ovarian cancer cells. Also, MMP-9 inhibits tumor growth in mice. MMP-9 gene RNAi inhibits migration, proliferation, and invasion.

B-cells generate MMP-9 destroying extracellular and membrane-attached materials. MMP receptor binding induces STAT3 phosphorylation and intracellular survival signals. (Redondo-Muñoz et al., 2010) Anti-MMP therapy can be beneficial for medulloblastoma cancer cells by intervening RNA sequence of the MMP-9 gene. Cell cycle arrest in the G0-G1 phase induced by MMP-9 is intermediate by the ERK/MAPK pathway that increases p16 expression. (Bonine-Summers et al., 2007)MMPs are a family of calcium-dependent zinc-containing endopeptidases, they have non-proteolytic activities besides extracellular matrix degradation.

Dufour (2008) assessed the epithelial cell migration task of pro-MMPs. MAPK and PI3K pathways. Homodimer formation is required for pro-MMP-9 cell migratory function. (Dufour et al., 2008)

Rac1 proteins affect cell migration and invasion by increasing endogenous ROS. (Sheikh et al., 2017) Histone modifications and chromatin-remodeling motors regulating gene expression are manipulating the expression of MMPs -enzymes that cleave protein substrates. mRNA stability besides transcriptional control and protein translation are also involved in MMPs regulation. (Legrand et al., 1999)

MMP-2 has an important role in angiogenesis, complete active form encourages apoptosis and inhibits neovascularization, while an intermediate activated form improves cell survival and angiogenesis. Migration by degradation of the basement membrane leads to the formation of new blood vessels. MMP-2 expression is not increased because of the binding of transcription factors because the MMP-2 gene lakes the binding site, unlike the MMP-9 gene. MMP-2 is activated by thrombin and activated protein C. MMP-2 may have an interchangeable function with MMP-9. Like MMP-2, MMP-9 can process cytokines and chemokine. MMP-9 size is larger than MMP-2. MMP-9 releases the biologically active form of VEGF, which is important in angiogenesis.

Figure 2 illustrates the role of MMPs in cancer. (Legrand et al., 1999)

Figure 3 demonstrated the cross-link between different pathways could be possessed by BHMC.

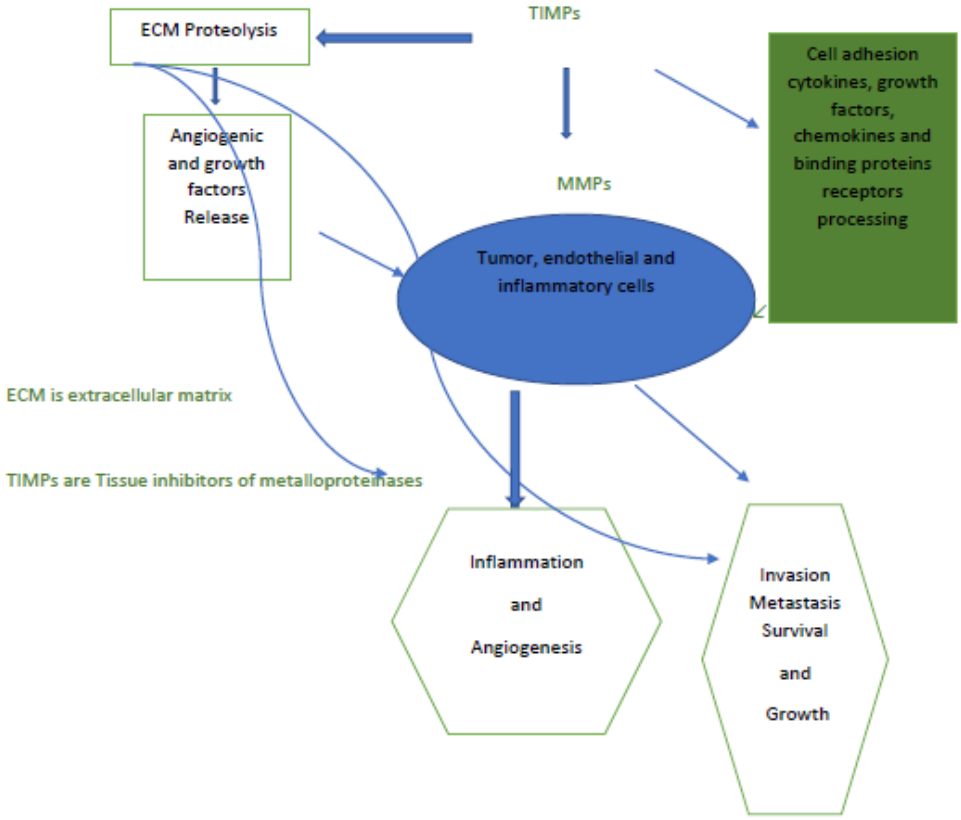


Figure 2: Role of MMPs in cancer.

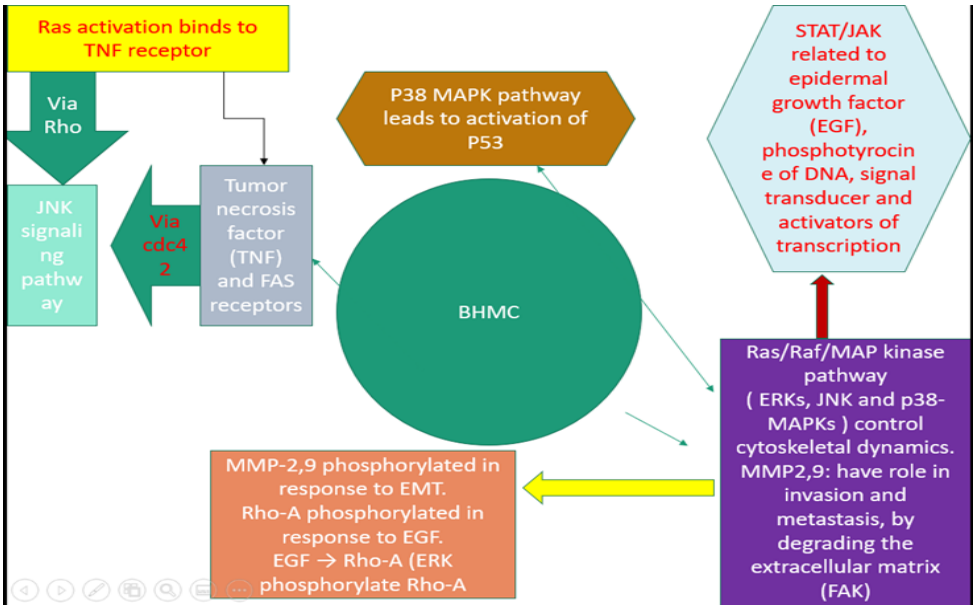


Figure 3: Illustrated the crosslink between different pathways could be possess by BHMC.

Methodology: PRISMA framework

1- Identification: keywords, search criteria/databases, records extracted.
2- Screening: inclusion and exclusion criteria
3- Eligibility: quality assessment (duplicate, out of scope, not suitable)
4- Included: the final number of articles included in the research.

Reporting

1- Search strategy

For this systemic search, we developed a search strategy to identify relevant literature, this search strategy was tailored to four databases: Scopus, web of sciences, since direct and google schooler. The search terms used are "BHMC"," Ras/Raf/MAP Kinase", "ERKs"," JNK", "P38-MAPKs", "STAT" and "MMP", all searched spanned from database inception until 2021 included article and review published in English only.

2- Selection criteria

The selection criteria were based on the PRISMA statement (Moher et al., 2009), the search mainly focused on mapping existing literature on "curcumin"," Ras/Raf/MAP Kinase", "ERKs"," JNK", "P38-MAPKs", "STAT" and "MMP" in the field of Biochemistry, Genetics and Molecular Biology, Medicine, Pharmacology and Toxicology and Pharmaceutics, the search span were from 2017-2021, the articles before 2017 were excluded. A total of 3050 articles were excluded, there were 219 recorded at this stage.

3- Quality assessment

The study is based on Review and Article, all duplications were corrected. In the review process, analysis and purification of articles are done by checking abstracts, to ensure the relevance and quality of academic literature included, we limited papers published to English language only. Then filtration of duplicate records, 10 more articles were removed from the study, after evaluating each article on the exclusion and inclusion criteria we picked 50 articles.

Figure1 showed the literature exclusion and inclusion criteria at each stage. (PRISMA statement)

4- Data extraction

In the data extraction phase, 50 articles were selected, and the characteristics extracted were:

- Article must be original paper or review paper, Conference Paper, Letter and Short Survey were excluded.
- The article should be in English language and from fields of Biochemistry, Genetics and Molecular Biology, Medicine, Pharmacology, Toxicology and Pharmaceutics.
- Extracted articles were published between 2017-2021.
- Irrelevant, out of scope, and not related articles were removed.

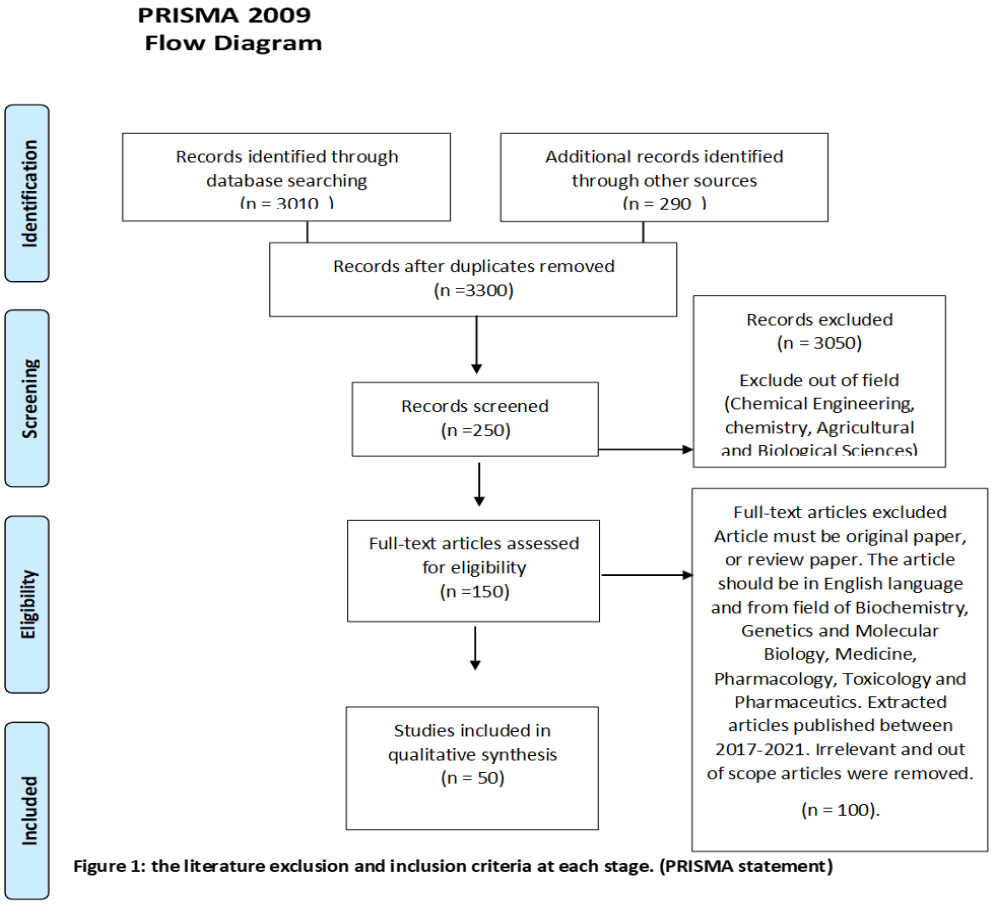


Figure 1: the literature exclusion and inclusion criteria at each stage. (PRISMA statement)

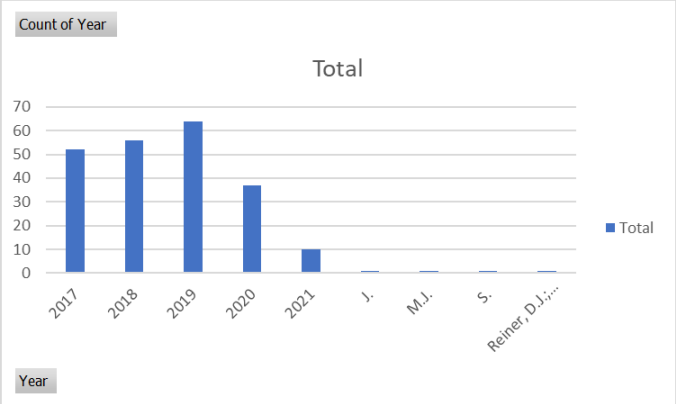


Figure-4: histogram of year vs count of year.

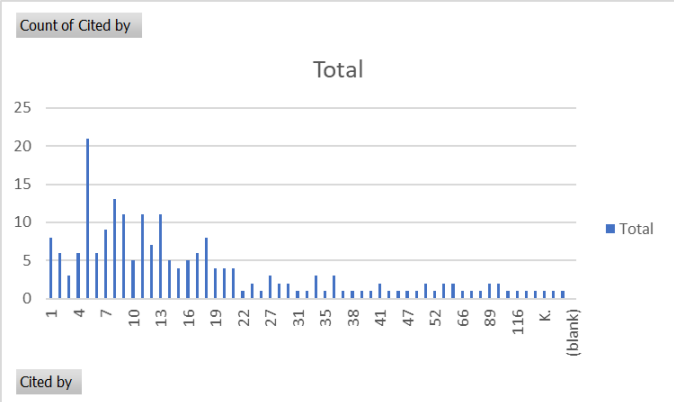


Figure 5: diagram of cited by vs count of cited by.

RESULTS AND INTERPRETATIONS

1- Descriptive analysis

Year and citation distribution were studied, showing the relations in figures 4 & 5.

Figure 4 shows that 2019 is the highest year count, while figure 5 shows the relationship of "cited by" vs "the sum of cited by" shows the number of cumulative citations, figure 5 shows that the highest count of cites is 20.

Figure 4 is the histogram of year vs sum of years showing number of publications while Figure 5 is the Cited by vs sum of cited showing the number of citations.

2- literature classification was studied based on the pathways possessed by antitumor agents used to kill cancer cells.

CONCLUSION AND FUTURE AGENDA

1. Deep molecular study of the tumor suppression and oncoproteins function of JNK and p38 MAPK family members is needed together with physiological implications resulting from crosstalk between these signaling pathways.
2. When, where and how precise targeting of the JNK and p38 MAPK pathways in therapeutic applications should be determined. Pointing genes or isoforms of JNK and p38 MAPK is better than pointing the whole pathway.
3. More understanding of PAKs role in cell transformation is a target for therapeutic purposes.
4. Rac1/ ROS/MAPK/AP-1 pathway regulation and inhibiting MMPs are important targets in tumor therapy.

Table 1: Summarizes the effect of curcumin and its analogs on multiple cancer cells with correlated pathways, it gives information extracted from studies done using curcumin and its derivatives.

Author's name	Cancer type	Process affected	Curcumin derivative	Pathway studied	Tests used	Findings
1. (Harun et al., 2018)	breast cancer cells (MDA-MB-231).	Metastasis, invasion and migration,	BHMC	decrease expressions of MT1-MMP, Rho guanine nucleotide exchange factor 7 and MMP-9.	invasion, scratch migration assays and transwell migration	12.5 μM BHMC preventing breast cancer invasion as an optimum concentration.
2.(Yoysungnoen et al., 2008)	HCC Hep G2 cell lines	angiogenesis	curcumin and tetrahydro curcumin	Capillary vascularization	Mtt assay	Anti-cancer effect is due to anti-angiogenesis properties of CUR and THC.
3.(Yeap, 2021)	MCF-7 breast cancer	Metastasis, invasion and apoptosis	BHMC	miRNAs and associated genes.	Cell viability, cell cycle, apoptotic assays and qPCR	BHMC induces apoptosis via affecting miRNAs and associated genes.
4.(Siwak et al., 2005)	melanoma cell lines (C32, G-361, and WM 266-4)	proliferation and apoptosis	curcumin	NF-kB and IKK activities	flow-cytometry and (3-[4,5-dimethylthiazol-2-yl]2,5-diphenyltetrazolium bromide assay	Curcumin suppresses NF-kB and IKK pathways independently of Raf/MEK/ERK and Akt pathways. It is potent antiproliferative and proapoptotic agent in melanoma cells.
5.(Alwi et al., 2019)	Human Liver Cancer Cells, HepG2	Apoptosis (viability)	Curcumin and BHMC	Cell morphology and viability	MTT assay and trypan blue assay	BHMC more cytotoxic on HepG2 than curcumin with non-selective cytotoxicity on normal cells.
6.(Ye et al., 2016)	human lung cancer H460 cells	Apoptosis	double carbonyl analog of curcumin (A17) and Curcumin	Act on some components in (ER) stress-mediated apoptosis pathway	flow cytometry, western blot analysis, Colony formation and mtt assays.	A17 affecting ER stress-mediated mechanism with more stability and antitumor activity than curcumin in H460 cells.
7.(Razak et al., 2017)	4T1 breast cancer cells	apoptosis, proliferatio, inflammation and metastasis	Curcumin and BHMC	MMP-9, NF-Kb And TNF	Mtt assay and RT- q PCR	BHMC more potent as antitumor agent than curcumin

8.(Lee et al., 2015)	oral squamous cell carcinoma (OSCC)	progression and metastasis	curcumin	cell proliferation, invasion, and expression of MMPs and EMT regulators (EMT markers, such as Snail, Twist, and E-cadherin, and induced p53 expression)	Matrigel invasion chamber, trypan blue exclusion, and immunoblotting for detecting levels of proteins.	curcumin treatment controlled EMT markers expression, inhibits invasiveness in oral cancer and decreased expression of MMP-2,9.
9.(Chiu & Su, 2009)	MDA-MB-231 breast cancer cells	Proliferation and Apoptosis	Curcumin	protein expressions of p21, 53, Bax to Bcl-2 ratio, and NF-κBp65 expression	Western blot and mtt assay	curcumin inhibited migration of MDA-MB-231 cells by decreased expression of NF-κBp65 and induced apoptosis via up-regulating the Bax to Bcl-2 ratio.
10.(Santosh k. Sandur, (Tham et al., 2015)7)	DU145, U937, SCC-4, Jurkat-T-cell leukemia, H1299, KBM-5, Panc-1, Calu-6, A549, MCF-7, and A293	proliferation	Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones	TNF, NF-Kb, cytokines and ROS independent mechanism.	HPLC and western blot analysis.	Curcumin analoges exhibit different antiproliferative activity not related to ROS status.

Table-1: Information extracted from studies done using curcumin and its derivatives.

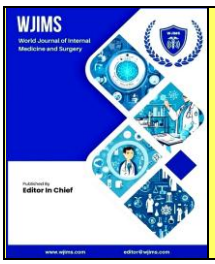
REFERENCES

1. Aggarwal, B. B., & Harikumar, K. B. (2009). Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. In International Journal of Biochemistry and Cell Biology (Vol. 41, Issue 1). https://doi.org/10.1016/j.biocel.2008.06.010
2. Alwi, S. S. S., Zahari, S., Haron, A. S., & Alexander, H. R. (2019). Cytotoxic Effect of 2,6-bis(4-Hydroxy-3-Methoxybenzylidene) cyclohexanone (BHMC) and Curcumin on Human Liver Cancer Cells, HepG2. Malaysian Journal of Medicine and Health Sciences, 15(July): 44–50.
3. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Mol Pharm., 2007; 4(6): 807–18.
4. Article O. Cytotoxic Effect of 2, 6-bis (4-Hydroxy-3-Methoxybenzylidene) cyclohexanone (BHMC) and Curcumin on Human Liver Cancer. maiaysian J Med Heal Sci., 2019; 2(July): 44–50.
5. Artym V V., Zhang Y, Seillier-Moiseiwitsch F, Yamada KM, Mueller SC. Dynamic interactions of cortactin and membrane type 1 matrix metalloproteinase at invadopodia: Defining the stages of invadopodia formation and function. Cancer Res., 2006; 66(6): 3034–43.
6. Bauvois B, Dumont J, Mathiot C, Kolb JP. Production of matrix metalloproteinase-9 in early stage B-CLL: Suppression by interferons. Leukemia, 2002; 16(5): 791–8.
7. Bonine-Summers, A. R., Aakre, M. E., Brown, K. A., Arteaga, C. L., Pietenpol, J. A., Moses, H. L., & Cheng, N. Epidermal growth factor receptor plays a significant role in hepatocyte growth factor mediated biological responses in mammary epithelial cells. Cancer Biology and Therapy, 2007; 6(4): 561–570. https://doi.org/10.4161/cbt.6.4.3851
8. Chen QY, Jiao DEM, Yao QH, Yan J, Song J, Chen FY, et al. Expression analysis of Cdc42 in lung cancer and modulation of its expression by curcumin in lung cancer cell lines. Vol. 40, International Journal of Oncology, 2012; 1561–8.
9. Chiu TL, Su CC. Curcumin inhibits proliferation and migration by increasing the Bax to Bcl-2 ratio and decreasing NF-κBp65 expression in breast cancer MDA-MB-231 cells. International Journal of Molecular Medicine, 2009; 23: 469–75.
10. Dai, R., Chen, R., & Li, H. Cross-talk between PI3K/Akt and MEK/ERK pathways mediates endoplasmic reticulum stress-induced cell cycle progression and cell death in human hepatocellular carcinoma cells. International Journal of Oncology, 2009; 34(6): 1749–1757. https://doi.org/10.3892/ijo_00000306
11. Duff Putu, Jean Shoveller., Julio Montaner., Cindy Feng., Rachel Nicoletti., Kate Shannon. GO. Curcumin-encapsulated nanoparticles as innovative. Physiol Behav, 2016; 176(1): 139–48.
12. Dufour, A., Sampson, N. S., Zucker, S., & Cao, J. Role of the hemopexin domain of matrix metalloproteinases in cell migration. Journal of Cellular Physiology, 2008; 217(3): 643–651. https://doi.org/10.1002/jcp.21535
13. Fini ME, Cook JR, Mohan R, Brinckerhoff CE. Regulation of Matrix Metalloproteinase Gene Expression. Matrix Metalloproteinases, 1998; 299–356.
14. Garcea, G., Berry, D. P., Jones, D. J. L., Singh, R., Dennison, A. R., Farmer, P. B., Sharma, R. A., Steward, W. P., & Gescher, A. J. Consumption of the putative chemopreventive agent curcumin by cancer patients: Assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiology Biomarkers and Prevention, 2005; 14(1): 120–125.
15. Harun SNA, Israf DA, Tham CL, Lam KW, Cheema MS, Hashim NFM. The molecular targets and anti-invasive effects of 2,6-bis-(4-hydroxyl-3methoxybenzylidine) cyclohexanone or BHMC in MDA-MB-231 human breast cancer cells. Molecules, 2018; 23(4): 18.
16. Hassani A, Mahmood S, Enezei HH, Hussain SA, Hamad HA, Aldoghachi AF, et al. Formulation, characterization and biological activity screening of sodium alginate-gum Arabic nanoparticles loaded with curcumin. Molecules, 2020; 25(9).
17. Idiiatullina E, Al-Azab M, Walana W, Pavlov V, Liu B. EnDuo, a novel derivative of Endostar, inhibits the migration of colon cancer cells, suppresses matrix metalloproteinase-2/9 expression and impedes AKT/ERK activation. Vol. 134, Biomedicine and Pharmacotherapy, 2021.
18. Klein T, Bischoff R. Physiology and pathophysiology of matrix metalloproteases. Amino Acids., 2011; 41(2): 271–90.
19. Lee AYL, Fan CC, Chen YA, Cheng CW, Sung YJ, Hsu CP, et al. Curcumin Inhibits Invasiveness and Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma Through Reducing Matrix Metalloproteinase 2, 9 and Modulating p53-E-Cadherin Pathway. Integr Cancer Ther., 2015; 14(5): 484–90.
20. Lee YZ, Ming-Tatt L, Lajis NH, Sulaiman MR, Israf DA, Tham CL. Development and validation of a bioanalytical method for quantification of 2,6-Bis-(4-hydroxy-3-methoxybenzylidene)-cyclohexanone (BHMC) in rat plasma. Vol. 17, Molecules, 2012; 14555–64.
21. Legrand, C., Gilles, C., Zahm, J. M., Polette, M.,

Buisson, A. C., Kaplan, H., Birembaut, P., & Tournier, J. M. Airway epithelial cell migration dynamics: MMP-9 role in cell- extracellular matrix remodeling. Journal of Cell Biology, 1999; 146(2): 517–529. https://doi.org/10.1083/jcb.146.2.517

22. Mansouri K, Rasoulpoor SS, Daneshkhah A, Abolfathi S, Salari N, Mohammadi M, et al. Clinical effects of curcumin in enhancing cancer therapy: A systematic review. BMC Cancer, 2020; 20(1): 1–11.
23. Meng L, Ji R, Dong X, Xu X, Xin Y, Jiang X. Antitumor activity of ginsenoside Rg3 in melanoma through downregulation of the ERK and Akt pathways. International Journal of Oncology, 2019; 54: 2069–79.
24. Ming-Tatt L, Khalivulla SI, Akhtar MN, Mohamad AS, Perimal EK, Khalid MH, et al. Antinociceptive Activity of a Synthetic Curcuminoid Analogue, 2,6-bis-(4-hydroxy-3-methoxybenzylidene)cyclohexanone, on Nociception-induced Models in Mice. Basic and Clinical Pharmacology and Toxicology, 2012; 110: 275–82.
25. Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ (Online), 2009; 339(7716): 332–336. https://doi.org/10.1136/bmj.b2535
26. Motterlini R, Foresti R, Bassi R, Green CJ. Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress. Free Radic Biol Med., 2000; 28(8): 1303–12.
27. O'Grady, S., & Lawless, M. W. (2015). Liver Cancer (Hepatocellular Carcinoma). In Epigenetic Cancer Therapy. Elsevier Inc. https://doi.org/10.1016/B978-0-12-800206-3.00012-4
28. Parvathy KS, Negi PS, Srinivas P. Antioxidant, antimutagenic and antibacterial activities of curcumin-ß-diglucoside. Food Chem [Internet], 2009; 115(1): 265–71. Available from: http://dx.doi.org/10.1016/j.foodchem.2008.12.036
29. Properties, M. (2006). curcumin— Biological and Medicinal Properties. In Vivo, March 2016; 297–368.
30. Rao JS, Bhoopathi P, Chetty C, Gujrati M, Lakka SS. MMP-9 short interfering RNA induced senescence resulting in inhibition of medulloblastoma growth via p16INK4a and mitogen-activated protein kinase pathway. Cancer Res., 2007; 67(10): 4956–64.
31. Razak NA, Akhtar MN, Abu N, Ho WY, Tan SW, Zareen S, et al. The: In vivo anti-tumor effect of curcumin derivative (2 E,6 E)-2,6-bis(4-hydroxy-3-methoxybenzylidene)cyclohexanone (BHMC) on 4T1 breast cancer cells., RSC Advances, 2017; 7: 36185–92.
32. Redondo-Muñoz, J., Ugarte-Berzal, E., Terol, M. J., Van den Steen, P. E., Hernández del Cerro, M., Roderfeld, M., Roeb, E., Opdenakker, G., García-Marco, J. A., & García-Pardo, A. Matrix Metalloproteinase-9 Promotes Chronic Lymphocytic Leukemia B Cell Survival through Its Hemopexin Domain. Cancer Cell, 2010; 17(2): 160–172. https://doi.org/10.1016/j.ccr.2009.12.044
33. Ricky A. Sharma. Phase I Clinical Trial of Oral Curcumin _ Clinical Cancer Research. clinical cancer research, 2004; 6847–54.
34. Roxburgh, P., & Jeffry Evans, T. R. (2008). Systemic therapy of hepatocellular carcinoma: Are we making progress? Advances in Therapy, 25(11): 1089–1104. https://doi.org/10.1007/s12325-008-0113-z
35. Santosh k. Sandur. (2007). Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin andturmerones differentially regulate anti-inflammatory and anti-proliferative responsesthrough a ROS-independent mechanism.pdf (pp. 1765–1773). carcinogenesis.
36. Sheikh, B. Y., Sarker, M. M. R., Kamarudin, M. N. A., & Ismail, A. Prophetic medicine as potential functional food elements in the intervention of cancer: A review. Biomedicine and Pharmacotherapy, 2017; 95: 614–648. https://doi.org/10.1016/j.biopha.2017.08.043
37. Siwak DR, Shishodia S, Aggarwal BB, Kurzrock R. Curcumin-induced antiproliferative and proapoptotic effects in melanoma cells are associated with suppression of IκB kinase and nuclear factor κB activity and are independent of the B-Raf/mitogen-activated/ extracellular signal-regulated protein kinase pa. Cancer, 2005; 104(4): 879–90.
38. Szczepanowska, J. (2009). Involvement of Rac/Cdc42/PAK pathway in cytoskeletal rearrangements. In Acta Biochimica Polonica (Vol. 56, Issue 2). https://doi.org/10.18388/abp.2009_2453
39. Tham CL, Lam KW, Rajajendram R, Cheah YK, Sulaiman MR, Lajis NH, et al. The effects of a synthetic curcuminoid analogue, 2,6-bis-(4-hydroxyl-3- methoxybenzylidine)cyclohexanone on proinflammatory signaling pathways and CLP-induced lethal sepsis in mice. Eur J Pharmacol [Internet], 2011; 652(1–3): 136–44. Available from: http://dx.doi.org/10.1016/j.ejphar.2010.10.092
40. Tham, C. L., Hazeera Harith, H., Wai Lam, K., Joong Chong, Y., Singh Cheema, M., Roslan Sulaiman, M., Hj Lajis, N., & Ahmad Israf, D. The synthetic curcuminoid BHMC restores endotoxin-stimulated HUVEC dysfunction: Specific disruption on enzymatic activity of p38 MAPK. European Journal of Pharmacology, 2015; 749: 1–11. https://doi.org/10.1016/j.ejphar.2014.12.015

41. Tham, C. L., Liew, C. Y., Lam, K. W., Mohamad, A. S., Kim, M. K., Cheah, Y. K., Zakaria, Z. A., Sulaiman, M. R., Lajis, N. H., & Israf, D. A. A synthetic curcuminoid derivative inhibits nitric oxide and proinflammatory cytokine synthesis. European Journal of Pharmacology, 2010; 628(1–3): 247–254. https://doi.org/10.1016/j.ejphar.2009.11.053
42. Tham, C. L., Yeoh, S. Y., Ong, C. H., Harith, H. H., & Israf, D. A. (2021). A Synthetic Curcuminoid Analogue, 2,6-Bis-4-(Hydroxyl-3-Methoxybenzylidine)-Cyclohexanone (BHMC) Ameliorates Acute Airway Inflammation of Allergic Asthma in Ovalbumin-Sensitized Mice. Mediators of Inflammation, 2021. https://doi.org/10.1155/2021/9725903
43. Thomas, S. J., Snowden, J. A., Zeidler, M. P., & Danson, S. J. (2015). The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. British Journal of Cancer, 2015; 113(3): 365–371. https://doi.org/10.1038/bjc.2015.233
44. Tian R, Li X, Gao Y, Li Y, Yang P, Wang K. Identification and validation of the role of matrix metalloproteinase-1 in cervical cancer, International Journal of Oncology, 2018; 52; 1198–208.
45. Tong, J., Li, L., Ballermann, B., & Wang, Z. Phosphorylation and activation of RhoA by ERK in response to epidermal growth factor stimulation. PLoS ONE, 2016; 11(1): 1–26. https://doi.org/10.1371/journal.pone.0147103
46. Wang S, Yao Y, Rao C, Zheng G, Chen W. 25-HC decreases the sensitivity of human gastric cancer cells to 5-fluorouracil and promotes cells invasion via the TLR2/NF-κB signaling pathway. Int J Oncol, 2019; 54(3): 966–80.
47. Xu Y, Ma Y, Liu XL, Gao SL. MiR-133b affects cell proliferation, invasion and chemosensitivity in renal cell carcinoma by inhibiting the ERK signaling pathway., Molecular Medicine Reports, 2020; 22: 67–76.
48. Yang X, Li Z, Zhang L, He J, Sun LQ. Selection and antitumor activity of anti-Bcl-2 DNAzymes. Biochem Biophys Res Commun [Internet], 2016; 479(3): 544–50. Available from: http://dx.doi.org/10.1016/j.bbrc.2016.09.107
49. Ye H, Wei X, Wang Z, Zhang S, Ren J, Yao S, et al. A novel double carbonyl analog of curcumin induces the apoptosis of human lung cancer H460 cells via the activation of the endoplasmic reticulum stress signaling pathway. Oncol Rep., 2016; 36(3): 1640–8.
50. Yeap SK, Ali NM, Akhtar MN, Razak NA, Chong ZX, Ho WY, et al. Induction of apoptosis and regulation of MicroRNA expression by (2E,6E)-2,6-bis-(4-hydroxy-3-methoxybenzylidene)-cyclohexanone (BHMC) treatment on MCF-7 breast cancer cells. Molecules, 2021; 26(5): 15.
51. Yoysungnoen P, Wirachwong P, Changtam C, Suksamram A, Patumraj S. Anti-cancer and anti-angiogenic effects of curcumin and tetrahydrocurcumin on implanted hepatocellular carcinoma in nude mice. World J Gastroenterol, 2008; 14(13): 2003–9.
52. Yuan Y, Ye HQ, Ren QC. Upregulation of the BDNF/TrKB pathway promotes epithelial-mesenchymal transition, as well as the migration and invasion of cervical cancer. International Journal of Oncology, 2018; 52: 461–72.
53. Zhong, C., Qiu, S., Li, J., Shen, J., Zu, Y., Shi, J., & Sui, G. Ellagic acid synergistically potentiates inhibitory activities of chemotherapeutic agents to human hepatocellular carcinoma. Phytomedicine, 2019; 59(April): 152921. https://doi.org/10.1016/j.phymed.2019.152921
54. Zhou G, Peng F, Zhong Y, Chen Y, Tang M, Li D. Rhein suppresses matrix metalloproteinase production by regulating the Rac1/ROS/MAPK/AP-1 pathway in human ovarian carcinoma cells. Int J Oncol, 2017; 50(3): 933–41.
55. Zhou W, Yu X, Sun S, Zhang X, Yang W, Zhang J, et al. Increased expression of MMP-2 and MMP-9 indicates poor prognosis in glioma recurrence. Vol. 118, Biomedicine and Pharmacotherapy, 2019.
56. Zhu N, Xiang Y, Zhao X, Cai C, Chen H, Jiang W, et al. Thymoquinone suppresses platelet-derived growth factor-BB–induced vascular smooth muscle cell proliferation, migration and neointimal formation, Journal of Cellular and Molecular Medicine, 2019; 23: 8482–92.



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