Review article Available online www.ijrpsonline.com ISSN: 2249–3522

International Journal of Research in Pharmacy and Science

A Review on Therapeutic targets of aspirin that could be involved in CRC chemo-prevention

Mohammed Abujamal[1], Mariam Abdalla[2], Hind Almodaimegh[3], Senthilvel Vasudevan[4*]

[1]Lecturer, Pharmacy Practice Department, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard–Health Affairs. ahmedmo@ksau-hs.edu.sa
[2]Lecturer, Pharmacy Practice Department, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, , Ministry of National Guard–Health Affairs. abdallama@ksau-hs.edu.sa
[3]Associate Dean, College of Pharmacy- Female Branch King Saud Bin Abdulaziz University for Health Sciences, Cardiology Clinical Pharmacy Specialist, Program Director, Pharmacy Practice Residency-Cardiology King Abdulaziz Medical City.Modaimeghh@ksau-hs.edu.sa
[4]SenthilvelVasudevan, Ph. D., FRSS, Assistant Professor of Statistics,Department of Pharmacy Practice, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS), Ministry of National Guard Health Affairs, PO BOX 3163, Riyadh 11481, Saudi Arabia, Tel: +966 11 429 9999, Ext. 95008, **Email:** vasudevans@ksau-hs.edu.sa

ABSTRACT:

Our present review isfocused on different therapeutic targets of aspirin in colorectal cancer (CRC) chemo-prevention.

In our present review, the searching in the electronic data base was conducted through Pub Med, ScienceDirect, Cochrane Library, Scopus and Google Scholar, restricted to the studies from 2000 to 2015.This review focuses on the therapeutic targets of aspirin in (CRC) chemo-prevention. we describe the possible pathways through which aspirin could mediate its beneficial effects in CRC. These chemo-preventive mechanisms of action make aspirin an attractive treatment option for managing CRC.

Therapeutic targets of aspirin were observed, they were classified into cyclooxygenase-dependent; the adenomatous polyposis coli (APC)/beta-catenin-mediated oncogenic Wnt pathway, the phosphatidylinositol 3-kinase (PI3K) signalling pathway, the role of the non-steroidal anti-inflammatory activated gene-1 (NAG-1), inhibiting the generation of sphingosine-1-phosphate and other cyclo-oxygenase-dependent mechanisms and cyclooxygenase-independent pathways such as aspirin induces pro-apoptotic pathways and autophagy and microsatellite instability and mismatch repair (MMR).

Aspirin has different targets through which it exerts its chemo-preventive action, according to its relation to cyclooxygenase (COX) enzyme, they are classified into COX-dependent and COX-independent pathways, both may act synergistically at different levels.

KEY-WORDS: Aspirin, Acetylsalicylic acid, Acetylsalicylate, Chemoprevention and Colorectal cancer

Corresponding Author:-
Senthilvel Vasudevan, Ph. D., FRSS
Assistant Professor of Statistics, Department of Pharmacy Practice, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS), Ministry of National Guard Health Affairs, PO BOX 3163, Riyadh 11481, Saudi Arabia, Tel: +966 11 429 9999, Ext. 95008,
Email: vasudevans@ksau-hs.edu.sa

INTRODUCTION:

The molecular mechanisms underlying these effects are diverse. In particular, aspirin can function via two different types of pathway: cyclooxygenase-dependent and cyclooxygenase-independent pathways (both of which might function synergistically at different level).[1, 2-4] Because the etiology and pathophysiology of CRC is complex, it is unlikely that the chemo-preventive effect of aspirin can be explained by only one mechanism. Taking these mechanisms together may therefore offer an important insight into the beneficial effects of aspirin on CRC.

This review focuses on the therapeutic targets of aspirin in CRC chemo-prevention. we describe the possible pathways through which aspirin could mediate its beneficial effects in CRC.These chemo-preventive mechanisms of action make aspirin an attractive treatment option for managing CRC. The main objectives of our present review arefocused on different therapeutic targets of aspirin.

MATERIALS AND METHODS:

In our present review, the searching in the electronic data base was conducted through Pub Med, ScienceDirect, Cochrane Library, Scopus and Google Scholar, restricted to the studies from 2000 to 2015.This review focuses on the therapeutic targets of aspirin in (CRC) chemo-prevention. we describe the possible pathways through which aspirin could mediate its beneficial effects in CRC. These chemo-preventive mechanisms of action make aspirin an attractive treatment option for managing CRC.

RESULTS:

1. Therapeutic targets of aspirin that could be involved in CRC chemo-prevention:

A. Cyclooxygenase-dependent pathways:

1. The adenomatous polyposis coli (APC)/beta-catenin-mediated oncogenic Wnt pathway:

The most commonly mutated gene in CRC is the adenomatous polyposis coli (APC) gene, which encodes a known tumor suppressor protein.[5-9]The APC protein controls diverse cellular processes mainly through association with other proteins, especially those that are involved in cell attachment and signaling. One protein with which APC associates is β-catenin. Mutation of the APC gene allows for activation of the oncogenic Wnt/β-catenin pathway, subsequent cytosolic accumulation ofβ-catenin, and its translocation to the nucleus. In the nucleus, β-catenin functions as a cofactor for the stimulation of gene transcription.[4, 10, 11]It acts as a transcriptional co-activator for the expression of genes with T-cell factor/lymphoid enhancer family (TCF/LEF) binding sites in their regulatory DNA regions. Targets of this pathway include oncogenes (such as K-Ras), cell-cycle-regulating genes, growth factors (epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF)), peroxisome proliferator-activated receptors delta (PPAR delta), and cyclooxygenase-2 (COX-2), in addition to many others.[4, 10-12]

Upregulated expression of COX-2 stimulates the activation of co-carcinogens and leads to increased levels of prostaglandin E2 (PGE2), which functions in a positive feed-back loop to enhance the nuclear actions of β-catenin. PGE2 inhibits apoptosis and stimulates tumor growth as well as stimulates angiogenesis, and promotes immunosuppression in patients with CRC.[4, 13, 14]

Aspirin inhibits cyclooxygenase enzymes, which are responsible for catalyzing the key steps in the formation of prostaglandins and related eicosanoids.[15-17] In a study compared the effect of aspirin use on the risk of CRC in relation to the COX-2 expression, aspirin use significantly reduced the risk of CRC that over-expressed COX-2 (95%CI, 0.52-0.78).[18]

2. The phosphatidylinositol 3-kinase (PI3K) signaling pathway:

The phosphatidylinositol 3-kinase (PI3K) signaling pathway has also been shown to be involved in colorectal carcinogenesis. Mutations in *PIK3CA* (the gene encoding phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit alpha polypeptide) result in the up-regulation of PI3K and increase the activity of COX-2 (also known as prostaglandin-endoperoxide synthase 2 (PTGS2)) and prostaglandin E2 synthesis, thus leading to the inhibition of apoptosis in colon cancer cells.[19, 20] Aspirin blocks the PI3K pathway, thereby leading to the suppression of cancer cell growth and to the induction of apoptosis.[4, 19] The effect of aspirin on the prognosis of CRC and associated-mortality wasassessed among 964 colorectal cancer patients, with either wild-type *PIK3CA* or mutated *PIK3CA*.[19] Regular use of aspirin significantly improved the survival of patients with mutated-*PIK3CA* colorectal cancer (multivariate hazard ratio (HR) for cancer-related death, 0.18; 95% CI, 0.06 - 0.61; P<0.001)and overall survival (multivariate HR for death from any cause, 0.54; 95% CI, 0.31 - 0.94; P=0.01).[19]

3. The role of the non-steroidal anti-inflammatory activated gene-1 (NAG-1):

Non-steroidal anti-inflammatory activated gene-1(NAG-1)is a member of the transforming growth factor beta(TGF-β) super family.[21]It has a multifunctional role and regulates several biological events, including bone formation, stress responses, hematopoietic development, adipose tissue function, apoptosis, and tumorigenesis.[21, 22] In CRC cells, NAG-1 expression is positively correlated with apoptosis and is inversely correlated with COX-2 expression.[21, 23] Increased COX-2 expression in colorectal tumors suppresses the expression of NAG-1. Aspirin treatment induces the expression of NAG-1, which contributes to its chemopreventive action. [21, 23]

4. Inhibiting the generation of sphingosine-1-phosphate:

Another cyclooxygenase-related mechanism of aspirin in CRC chemoprevention is its ability to inhibit sphingosine kinase. Sphingosine kinase generates the major product sphingosine-1-phosphate (S1-P), which mediates angiogenesis, metastasis and resistance of tumor cells to drug-induced apoptosis.[24]Approximately 50% of S1-P in blood is stored in circulating platelets and is released in a

thromboxane-dependent manner.[25]Aspirin markedly inhibits thromboxane-dependent S1-P release from human platelets at antiplatelet doses.[1, 4, 26]

5. Other cyclo-oxygenase-dependent mechanisms:

Aspirin and other non-steroidal anti-inflammatory drugs are well known inhibitors of cyclooxygenase enzymes. However, aspirin is unique in that it can acetylate the cyclooxygenase-2 enzyme, thus resulting in the generation of aspirin-triggered lipoxin (ATL), a protein with anti-inflammatory and anti-tumorigenic functions.[4, 27]

COX-2 also promotes carcinogenesis via the peroxidase activity of the PGH-synthase-complex. This peroxidase has broad substrate specificity and can use many substrates for co-oxidation. These metabolic transformations generate free radicals, which bind to DNA and potentially alter gene transcription.[4] At low doses, aspirin functions mainly by irreversible inactivation of platelet COX-1 activity.[17] Platelet activation is involved in the early stages of CRC through induction of a COX2-mediated paracrine signaling pathway between stromal cells and epithelial cells within adenomas.[2, 17]

B. Cyclooxygenase-independent pathways:

I. Aspirin induces pro-apoptotic pathways and autophagy:

The nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) is a transcriptional regulator that controls the expression of many genes involved in cell division and apoptosis. NFκB is normally sequestered in the cytoplasm, where it is bound by the inhibitor of κB (IκB), a family of inhibitory proteins. Aspirin induces IκB-degradation, which leads to NFκB activation. NFκB activation and nuclear translation results in enhanced apoptosis.[1, 4, 28, 29]

Aspirin also sensitizes tumor cells totumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which might act synergistically with the inhibition of COX-2-dependent prostaglandin formation. Thus, inhibition of prostaglandin production by aspirin might sensitize tumor cells for apoptosis and help to overcome their resistance against apoptotic stimuli.[30, 31] The mammalian target of rapamycin (mTOR) regulates cell growth, proliferation, motility, survival, protein synthesis, and transcription. Aspirin inhibits mTOR signaling and induces autophagy (a feature of mTOR inhibition). These actions may contribute to its protective effects against the development of CRC.[32]

II. Microsatellite instability and mismatch repair (MMR):

Aspirin has been found to promote genetic selection for microsatellite stability in human CRC cells deficient for a subset of mismatch repair (MMR) genes.[33] DNA microsatellite instability associated with dysfunction of MMR genes is frequent in hereditary nonpolyposis CRC (Lynch syndrome). Aspirin prevents oxidative DNA-strand breaks, and thereby has a protective role against DNA instability.[34]

CONCLUSION:

Aspirin has different targets through which it exerts its chemo-preventive action, according to its relation to cyclooxygenase (COX) enzyme, they are classified into COX-dependent and COX-independent pathways, both may act synergistically at different levels.

Conflicts of Interest:

The authors have no conflicts of interest to declare.

Funding information:

No financial support for this review that could have influenced its outcome.

REFERENCES:

1. Garcia-Albeniz X, Chan AT. Aspirin for the prevention of colorectal cancer. Best Pract Res ClinGastroenterol. 2011;25(0):461-72. PMID: 22122763
2. Bruno A DM, Tacconelli S, Patrignani P. Mechanisms of the antitumoural effects of aspirin in the gastrointestinal tract. Best Practice & Research Clinical Gastroenterology. 2012;26(4):e1-e13. **PMID:** 23199511
3. Ferrandez A, Piazuelo E, Castells A. Aspirin and the prevention of colorectal cancer. Best Pract Res ClinGastroenterol. 2012;26(2):185-95. Epub 2012/05/01. **PMID:** 22542156
4. Schror K. Pharmacology and cellular/molecular mechanisms of action of aspirin and non-aspirin NSAIDs in colorectal cancer. Best Pract Res ClinGastroenterol. 2011;25(4-5):473-84. Epub 2011/11/30. **PMID: 22122764**
5. RA W. The Biology of Cancer. Baltimore, MD. Garland Science. 2006. **PMID:**
6. De Filippo C, Luceri C, Caderni G, Pacini M, Messerini L, Biggeri A, et al. Mutations of the APC gene in human sporadic colorectal cancers. Scand J Gastroenterol. 2002;37(9):1048-53. Epub 2002/10/11. **PMID:** 12374230
7. Powell SM, Zilz N, Beazer-Barclay Y, Bryan TM, Hamilton SR, Thibodeau SN, et al. APC mutations occur early during colorectal tumorigenesis. Nature. 1992;359(6392):235-7. Epub 1992/09/17. **PMID:** 1528264
8. Cottrell S, Bicknell D, Kaklamanis L, Bodmer WF. Molecular analysis of APC mutations in familial adenomatous polyposis and sporadic colon carcinomas. Lancet (London, England). 1992;340(8820):626-30. Epub 1992/09/12. **PMID:** 1355210
9. Polakis P. The adenomatous polyposis coli (APC) tumor suppressor. Biochimica et biophysicaacta. 1997;1332(3):F127-47. Epub 1997/06/07. **DOI:** 10.1016/s0304-419X(97)00008-5
10. Reya T, Clevers H. Wntsignalling in stem cells and cancer. Nature. 2005;434(7035):843-50. Epub 2005/04/15. **PMID:** 15829953

11. Fodde R. The APC gene in colorectal cancer. Eur J Cancer (Oxford, England : 1990). 2002;38(7):867-71. Epub 2002/04/30. **PMID:** 11978510
12. Nuñez F, Bravo S, Cruzat F, Montecino M, De Ferrari GV. Wnt/β-Catenin Signaling Enhances Cyclooxygenase-2 (COX2) Transcriptional Activity in Gastric Cancer Cells. PLoS ONE. 2011;6(4):e18562. **PMID:** 21494638
13. Greenhough A, Smartt HJ, Moore AE, Roberts HR, Williams AC, Paraskeva C, et al. The COX-2/PGE2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment. Carcinogenesis. 2009;30(3):377-86. Epub 2009/01/13. **PMID:** 19136477
14. Brown JR, DuBois RN. COX-2: a molecular target for colorectal cancer prevention. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(12):2840-55. Epub 2005/04/20. **PMID:** 15837998
15. Barnes CJ, Hamby-Mason RL, Hardman WE, Cameron IL, Speeg KV, Lee M. Effect of aspirin on prostaglandin E2 formation and transforming growth factor alpha expression in human rectal mucosa from individuals with a history of adenomatous polyps of the colon. Cancer epidemiology, biomarkers &prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 1999;8(4 Pt 1):311-5. Epub 1999/04/20. **PMID:** 10207634
16. Frommel TO, Dyavanapalli M, Oldham T, Kazi N, Lietz H, Liao Y, et al. Effect of aspirin on prostaglandin E2 and leukotriene B4 production in human colonic mucosa from cancer patients. Clinical cancer research : an official journal of the American Association for Cancer Research. 1997;3(2):209-13. Epub 1997/02/01. **PMID:** 9815674
17. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. The New England journal of medicine. 2007;356(21):2131-Epub 2007/05/25. **PMID:** 17522398
18. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-Dose Aspirin for the Prevention of Atherothrombosis. New England Journal of Medicine. 2005;353(22):2373-83. **PMID:** 16319386
19. Chan AT, Ogino S, Fuchs CS. Aspirin and the Risk of Colorectal Cancer in Relation to the Expression of COX-2. New England Journal of Medicine. 2007;356(21):2131-42. **PMID:** 17522398
20. Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, et al. Aspirin Use, Tumor PIK3CA Mutation, and Colorectal-Cancer Survival. The New England journal of medicine. 2012;367(17):1596-606. **PMID:** 23094721

21. Whitehall VL, Rickman C, Bond CE, Ramsnes I, Greco SA, Umapathy A, et al. Oncogenic PIK3CA mutations in colorectal cancers and polyps. International journal of cancer Journal international du cancer. 2012;131(4):813-20. Epub 2011/09/21. **PMID:** 21932420
22. Wang X, Baek SJ, Eling TE. The diverse roles of nonsteroidal anti-inflammatory drug activated gene (NAG-1/GDF15) in cancer. Biochemical pharmacology. 2013;85(5):597-606. Epub 2012/12/12. **PMID:** 23220538
23. Mimeault M, Batra SK. Divergent molecular mechanisms underlying the pleiotropic functions of macrophage inhibitory cytokine-1 in cancer. Journal of cellular physiology. 2010;224(3):626-35. Epub 2010/06/26. **PMID:** 20578239
24. Baek SJ, Wilson LC, Lee CH, Eling TE. Dual function of nonsteroidal anti-inflammatory drugs (NSAIDs): inhibition of cyclooxygenase and induction of NSAID-activated gene. The Journal of pharmacology and experimental therapeutics. 2002;301(3):1126-31. Epub 2002/05/23. **PMID:** 12023546
25. Pyne NJ, Pyne S. Sphingosine 1-phosphate and cancer. Nat Rev Cancer. 2010;10(7):489-503. **PMID:** 20555359
26. Ulrych T, Bohm A, Polzin A, Daum G, Nusing RM, Geisslinger G, et al. Release of sphingosine-1-phosphate from human platelets is dependent on thromboxane formation. Journal of thrombosis and haemostasis: JTH. 2011;9(4):790-8. Epub 2011/01/22. **PMID: 21251196**
27. Schror K, Rauch B. [Aspirin in primary and secondary prevention of colorectal carcinomas]. MedizinischeMonatsschrift fur Pharmazeuten. 2013;36(11):411-21. Epub 2014/03/20. AcetylsalicylsaurezurPrimar- und SekundarpraventionkolorektalerKarzinome. **PMID:**
28. Janakiram NB, Rao CV. Role of lipoxins and resolvins as anti-inflammatory and proresolving mediators in colon cancer. Current molecular medicine. 2009;9(5):565-79. Epub 2009/07/16. **PMID:** 19601807
29. Jana NR. NSAIDs and apoptosis. Cellular and molecular life sciences: CMLS. 2008;65(9):1295-301. Epub 2008/02/23. **PMID:** 18292966
30. Din FVN, Stark LA, Dunlop MG. Aspirin-induced nuclear translocation of NFκB and apoptosis in colorectal cancer is independent of p53 status and DNA mismatch repair proficiency. British Journal of Cancer. 2005;92(6):1137-43. **PMID:** 15770215
31. Lu M, Strohecker A, Chen F, Kwan T, Bosman J, Jordan VC, et al. Aspirin sensitizes cancer cells to TRAIL-induced apoptosis by reducing survivin levels. Clinical cancer research: an official journal of the American Association for Cancer Research. 2008;14(10):3168-76. Epub 2008/05/17. **PMID:** 18483385

32. Kim KM, Song JJ, An JY, Kwon YT, Lee YJ. Pretreatment of acetylsalicylic acid promotes tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis by down-regulating BCL-2 gene expression. The Journal of biological chemistry. 2005;280(49):41047-56. Epub 2005/10/04. **PMID:** 16199534
33. Din FV, Valanciute A, Houde VP, Zibrova D, Green KA, Sakamoto K, et al. Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells. Gastroenterology. 2012;142(7):1504-15 e3. Epub 2012/03/13. **PMID:** 22406476
34. Goel A, Chang DK, Ricciardiello L, Gasche C, Boland CR. A novel mechanism for aspirin-mediated growth inhibition of human colon cancer cells. Clinical cancer research : an official journal of the American Association for Cancer Research. 2003;9(1):383-90. Epub 2003/01/23. **PMID:** 12538492