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Exploring the nutraceutical potential: Antioxidant and anti-inflammatory properties of *Momordica charantia*

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Abstract
Momordica charantia, commonly known as bitter melon, has been extensively utilized in traditional medicine for addressing various chronic inflammatory conditions, notably Diabetes mellitus. Many studies showed the potential of *Momordica charantia* in alleviating inflammation and oxidative stress, attributing its efficacy to its robust antioxidant and anti-inflammatory properties. The mechanistic insights reveal that these beneficial effects are primarily mediated through the down regulation of the NF-κB signaling pathway and the concurrent up regulation of the Nrf2 signaling pathway. Based on the study *Momordica charantia* as a promising therapeutic candidate for managing a spectrum of lifestyle-related diseases.

Keywords: *Momordica*, antioxidant, anti-inflammatory NF-Kb, Nrf-2

Introduction
Momordica charantia L. the plant being used for years in folk medicine with common as bitter melon or bitter gourd belongs to the family, Cucurbitaceae (Krawinkel & Kedig 2006) [2]. Being distributed widely in the areas Asia, South America and the African countries and also in the Caribbean and Amazon basin. The word *Momordica* in Latin implies as *"*to bite" due to the jagged leaf edges. Depending upon the size of the fruit, it has been divided into minima where fruit size is less than 5 cm. In contrary, it was categorized as maxima where fruit size is above 5 cm. *M. charantia* is generally cultivated for its fruit which is known for various medicinal properties (Basch *et al.*, 2003) [3]. The bitter taste is because of the presence of cucurbitane glycosides which are nontoxic and named as momordicoside K, momordicoside L, momordicine I, and momordicine II (Basch *et al.*, 2003) [3].
Various plant parts especially roots, tender twigs, flowers, fruits and seeds are commonly used as flavoring agents (Scartezzini and Speroni, 2000; Morgan & Midmore, 2002) [4, 5]. Immature fruits will be useful for culinary purpose, preparation of pickles and canned foods. In India, mostly in the culinary practice the fruits as well as the leaves are mostly used as treatment for diabetes, abdominal pain and for wound healing (Paul *et al*., 2009) [6]. Some people use leaf juice against for diabetes. It contains diuretic, laxative and anti-helminthic properties.

Chemical constituents of *Momordica charantia*
Momordica charantia exhibits many medicinal uses, as an anti-diabetic, hypercholesterolemia, hypotriglyceridemic, hypo-tensive agent, to boost the immune system as an immunostimulant, and even have the anti-viral, anti-inflammatory, antioxidant, antibacterial, anthelmintic, antimutagenic, anti-ulcer, anti-leukemic and also known for its insecticidal properties that were identified in different parts of *M. charantia* (Tan and Gan, 2016) [7].
The potential effects are greatly attributed to the Phytoconstituent chemicals present in all parts of MC and more specifically in fruit and seed such as flavonoids, steroids, saponins, glycosides, polysaccharides, fatty acids, alkaloids, triterpenoids, amino acids, essential oils.
For management of body weight and in regulating the lipid metabolism MC contains the vital agents such as Ribosome-Inactivating Proteins (RIPs), charantin, polypeptide-p and vicine henceforth used for the treatment of hyperglycaemia (Li *et al*., 2015) [42].

Anti-oxidant effects of *Momordica charantia*
Perumal *et al.* (2021) [9] reported many compounds with the antioxidant properties which Include 3- malonylmomordicin I, goyaglycoside G ascorbic acid, quer-cetin 3-O-glycoside,

kuguacin H, brevifolincarboxylic acid cucurbitacin E, margarolic acid.

Chokki *et al*. (2020) [10] reported that MC extract contains Chlorogenic acid, daidzein, epicatechin, rutin, quercetin, naringenin, genistein and naringin, as polyphenol compounds and the extracts with ethyl acetate exhibited inhibition against the enzyme α-amylase.

Jiang *et al*. (2020) [11] reported the increased activity of the enzymes SOD and CAT and the decreased malonaldehyde (MDA) levels in the pancreatic and liver tissue of the rats 4 weeks after administration of MC saponins (MCS) indicating that these MCS prevented the damage caused because of oxidative stress by enhancing the activity of antioxidant enzymes and reducing the lipid peroxidation.

Perez *et al*. (2019) [17] reported that the non-polar extracts of MC has got more inhibitory effect on the enzymes α-glucosidase and α-amylase, with pronounced inhibitory activity observed with chloroform and hexane extracts for α-glucosidase and the medium polar extracts inhibited α-amylase.

Gupta *et al.* (2019) [13] reported dose dependent inhibition of the enzyme pancreatic lipase from the ethanolic extract of MC.

Chanda *et al*. (2019) [14] reported positive correlation between phenolic content of ethyl acetate fraction of MC fruit extract and its pancreatic enzyme lipase inhibitory activity statistically, clearly demonstrating the role of phenolic compounds for higher inhibitory activity.

Biswas (2016) [15] concluded that the closely related pathophysiological processes inflammation and oxidative stress go hand in hand to activate each other. MC exhibited anti-inflammatory and anti-oxidant activities on a dose dependant manner (Chao *et al*., 2014) [28].

Shivanagoudra *et al.* (2019) [17] reported that the compounds of MC *viz*., 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al, charantal, charantoside XI, and 25ξ-isopropenylchole-5, 6-ene-3-O-d-glucopyranoside exhibited significant anti-inflammatory activity by downregulating the expression of NF-κB, iNOS, IL-6, IL-1β, TNF-α and Cox-2 in lipopolysaccharide-activated macrophage RAW 264.7 cells.

Liao *et al*. (2022) [18] demonstrated that the mcIRBP-9 a gastro-resistant peptide, from MC played a key role in altering the pathways of inflammation and immune responses where, NF-κB played a key role in the regulation of mcIRBP-9-affected pathways. Mc IRBP-9 from MC acted as a novel anti-inflammatory agent and also aids in renal protection.

Lii *et al*. (2009) [19] reported that *Momordica charantia* inhibited the production of LPS-induced Nitric oxide and PGE2 together with a reduction in the enzyme inducible NO synthase and IL-1β expression.

Padmashree *et al*. (2011) [20] concluded that the compounds with the antioxidant capacity id in bitter gourd exhibited the action through inhibition of lipid peroxidation. The cucurbitane-type triterpene glycosides of MC fruits significantly inhibited the xanthine oxidase activity (Lin *et al*., 2012) [76].

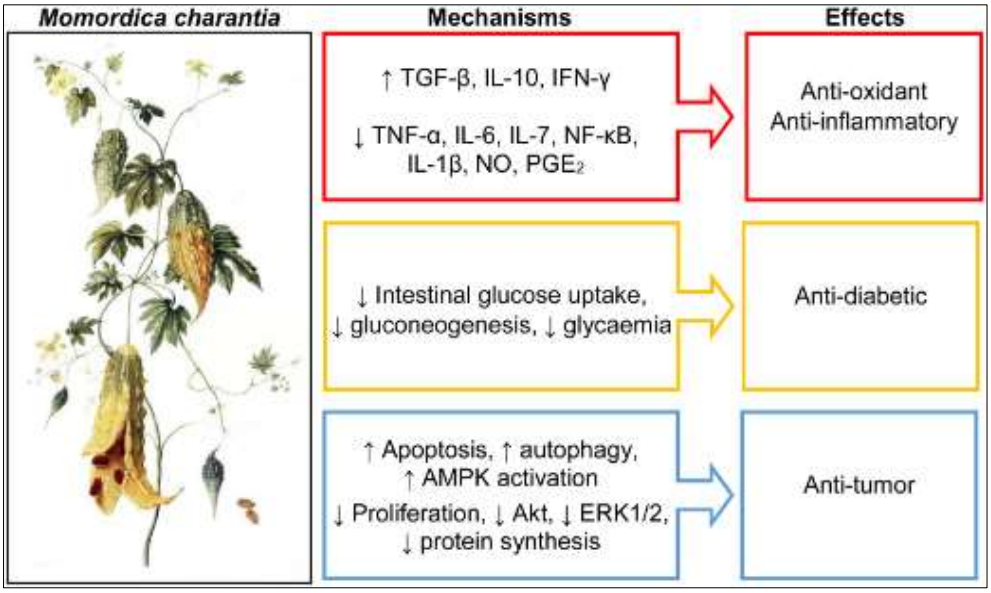

Fig 1: Mode of action of *Momordica charantia* (Bortolotti *et al*., 2019)

Yang *et al*. (2018) [23] in a study on murine macrophages reported that *Momordica charantia* reduced the expression levels of iNOS and cyclooxygenase-2 (COX-2), suppressing NF-κB, and activator protein-1 (AP-1) activity.

Bai *et al.* (2007) [22] in an *in vivo* study on high fat fed mice reported that the supplementation with MC powder lowered the systemic inflammation in obese mice by regulating the genes involved in inflammation and inturn reducing the serum levels of TNF-α and IL-6.

Yang *et al*. (2018) [23] reported that supplementation of MC extracts in TNF-α treated mice reduced the intercellular adhesion molecule-1 expression with decreased the PI3K/Akt/NF-kB/IkB.

Kim *et al.* (2018) [24] reported that pretreatment of neuroblastoma cells in an *in vitro* study with MC extracts was found to regulate the cytotoxic oxidative stress which was induced by H_2O_2 by enhancing the intracellular scavenging activity and by reducing the H_2O_2 -induced activation of the vital signaling pathway JNKs, p38, and ERK1/2 MAPK.

MC fruit extract significantly reduced the levels of SGOT and SGPT and also up regulated the genes expression encoding for the antioxidant enzymes SOD, CAT and GPx (Malekshahi *et al.*, 2019) [25].

Adelusi *et al.* (2021) [26] identified two vital compounds of MC (Catechin and Chlorogenic acid) which when bound to the Keap1 kelch domain and act as potential Nrf2 signalling activator through the downregulation of its Keap1 repressor during the *in-silico* research findings.

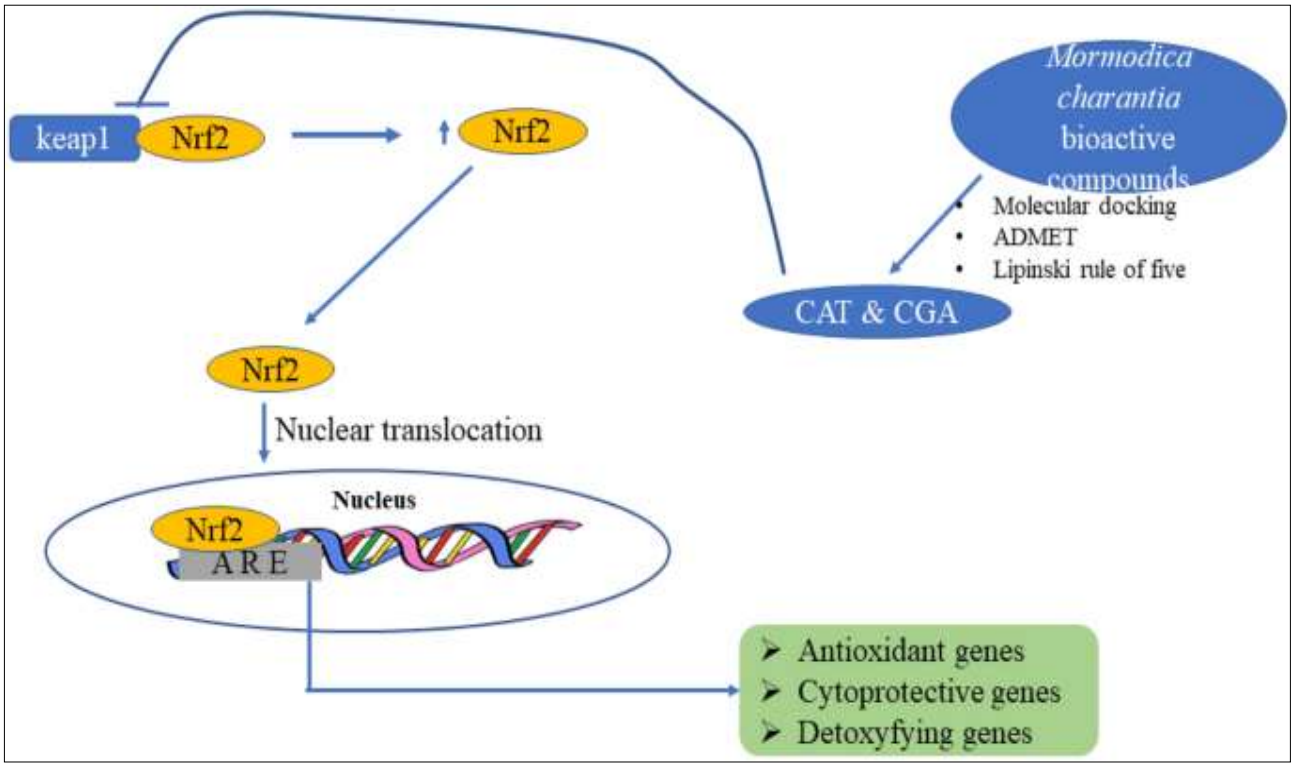

Fig 2: Antioxidant potential of Catechins and Chromogenic acid (Adelusi *et al*., 2021) [26]

Wang *et al*. (2017) [27] reported that the polysaccharide and saponins are the major bioactive substances which aid in significant improvement in the antioxidant capacity by enhancing the level of SOD and reducing the level of MDA and alleviate the STZ-induced tissue damage of kidney in the diabetic nephropathy condition by reducing the level of serum creatinine.

Anti-inflammatory effects of *Momordica charantia*

Momordica charantia contains PPARα and PPARγ activators which are known for maintaining the lipids in the blood and also exhibit anti-inflammatory activity (Ciou *et al*., 2014) [28]. The mechanisms exhibited at the molecular level is by inhibition of cytokines secreted by monocytes following PPARγ activation (Chao and Huang, 2003) [77] and interfere with the signaling of messages for NF-κB, by inhibiting the expression of vital inflammatory genes which code for IL-1, IL-2, IL-6, IL-8, TNF-α and matrix metalloproteinase (MMPs) (Mukherjee *et al*., 1994) [29]. PPARγ also reduces the activity of iNOS by inhibiting NFκB the transcription factor, thus alleviating inflammation (Ricote *et al*., 1998) [37]. Similarly, *Momordica charantia* significantly reduces the mediator of inflammation PGE_2 by decreasing the expression of COX-2 protein (Chao *et al*., 2014) [28]. *Momordica charantia* is mainly enriched with the vital flavonoid compounds such as charantins, and an increase in the anti-inflammatory properties noticed in *Momordica charantia* might be attributed to the presence of major active compounds such as charantosides (Abas *et al*., 2014) [31]. Anti-inflammatory activity noticed in the condition might be attributed to the production of 1, 25 (OH) $_2D_3$ during vitamin D metabolism and also *Momordica charantia* treatment lowered NF-κB, iNOS, COX-2, IL-6, IL-23, IL-1β, TNF-α and IFN-γ mRNA and protein levels (Shivanagoudra *et al*., 2019 and Acar *et al*., 2020) [17, 32]. *M. Charantia* extracts were found to lower the systemic inflammation in the body mainly by lowering the levels of TNF-α and IL-6 in the serum levels (Bai *et al*., 2007) [22]. The phytoconstituents present in the fruit effectively inhibited the mediators of inflammation, *viz*., PGE2 and nitric oxide (NO) (Hsu *et al*. 2011; Hsu *et al*. 2012 and Leung *et al*. 2009) [33, 34, 35]. Activation of PPARγ can attenuate the production inflammatory mediators like TNF-α, IL-6 and IL-1β (Hanada and Yoshimura, 2002) [36]. PPAR γ also can reduce the iNOS enzyme activity by inhibiting the activation of transcription factor NF-κB, henceforth alleviating the inflammation (Ricote *et al*. 1998) [37]. Bitter melon treatment reduced the production of pro-inflammatory cytokines and other substances and alleviate the inflammatory responses (Chao *et al*. 2014) [28]. Bitter melon treatment in IL-1β-treated hepatocytes deactivated the expression of iNOS protein. The extracts of bitter melon decreased the levels of iNOS mRNA indicating the inhibition of expression of the iNOS gene at the transcriptional level or later and also decreased the levels of mRNAs which code for pro-inflammatory cytokines (TNF-α and IL-6) and chemokines (CCL20 and CX3CL1). Also, suppressed the expression of TNF-α and IL-6 mRNA which play major role in chronic liver injury and inflammation. The cucurbitane-type triterpenoids, may be responsible for the anti-inflammatory effects of bitter melon (Dwijayanti *et al*. 2019) [38].

Table 1: Bioactive components, distribution and mode of action in *Momordica charantia*

Major Phytoconstituent	Biological Function	Part of the plant	Reference
Polysaccharides	Antioxidant, Neuroprotective, immune stimulant, antidiabetic, antitumorigenic	Vital plant parts	Xu *et al*. 2015 [39]; Zhang *et al*. 2016 [40]; Deng *et al*. 2014 [41]; Duan *et al*. 2015 [42]; Cai *et al*. 2010 [43] and Zhang *et al*. 2008 [40]
Peptides and proteins	RNA N-glycosidase, SOD, DNase-like, phospholipase, polynucleotide adenosine glycosidase (PAG), Anti-tumors, immune suppression.	Seed	Pu *et al*. 1996 [47]; Leung *et al*. 1997 [49]; Puri *et al*. 2009 [45]; Fang *et al*. 2012 [46]; Meng *et al*. 2012 [48]; Jabeen, U.; Khanum, 2017 [50] and Fang *et al*. 2012 [46].
Lipids	Antioxidant, Antitumor	Seed, flesh	Tsuzuki *et al*. 2004 [52]; Dhar *et al*. 2007 [51]; and Suzuki *et al*. 2010 [53].
Terpenoids	Antioxidant, Anticancer, hypoglycemic, antidiabetic, cancer chemoprevention	Stem, leave, fruit	Akihisa *et al*, 2007 [54]; Liu *et al*. 2010 [56]; Agrawal, and Beohar, 2010 [55]; Chou *et al*. 2015 [57].
Saponins	Antiviral, hypolip idemic, antihyperglycaemic,	Fruit, root, seed	Hsiao *et al*. 2013 [58]; Han *et al* 2008 [59]; Xia *et al*, 2007 [60]; Chang *et al*. 2004 [61]; Zhang *et al*. 2011 [62] and Patel *et al*. 2010 [63].
Phenolics	Antioxydant, immune enhancement, anti-inflammation,	Fruit, pericarp, seed	Anila and Vijayalakshmi, 2000 [64]; Bajpai *et al*, 2005 [66]; Qader *et al*., 2011 [65]; Lin and Tang, 2007 [67].
Sterols	Antimicrobial	Pericarp, fruit	Saeed and Tariq, 2005 [68]; Begum *et al*, 1997 [69]; Guevara *et al*, 1989 [70].

Table 2: Bioactive compounds of *Momordica charantia* under different groups

Group	Compounds	Distribution	Reference
Carotenoids	Zeaxanthin, β, α & β carotene, cryptoxanthin, lycopene, Lutein.	Fruit	Shubha *et al*. 2018 [71]
Cucurbitane Triterpenoids	Charantin & III, Karavilagenin A, B, C, D, E, saponins (triterpenoid glycosides), Goya saponins, saponins such as diosgenin	Leaves & ruits	Ullah *et al*. 2011 [72]; Li *et al*. 2015 [42]; Ingle & Kapgatte 2018 [73]; Ummi *et al*. 2018 [74]; Shubha *et al*. 2018 [71]; Mahwish *et al*. 2018 [78].
Phytosterols	campesterol, β sitosterol, decortinone, ergosterol peroxide, clerosterol, stigmasterol	Fruit	Ullah *et al*. 2011 [72]; Ummi *et al*. 2018 [74]; Shubha *et al*. 2018 [71]; Kim *et al*. 2013 [75].
Alkaloids		Fruits, Leaves & Seeds	Mahwish *et al*. 2018 [78]; Shubha *et al*. 2018 [71]; Ingle & Kapgate 2018 [73].

Conclusion

Momordica charantia which is been most commonly used since ages in traditional folk medicine for treating of various chronic ailments associated with metabolic disorders *viz*., Diabetes mellitus. Treatment with *Momordica charantia* could abrogate the changes observed in inflammation and oxidative stress owing to its antioxidant and anti-inflammatory potential mainly acted through down regulating of the nuclear factor- κB signaling pathway and up regulating the Nrf2 signaling pathway. Therefore, *Momordica charantia* could act as a promising avenue in the treatment of various life style diseases.

References

1. Marr KL, Mei XY, Bhattarai NK. Allozyme, morphological and nutritional analysis bearing on the domestication of *Momordica charantia* L. (Cucurbitaceae). Economic Botany. 2004;58:435-455.
2. Krawinkel MB, Keding GB. Bitter gourd (*Momordica charantia*): A dietary appraoach to hyperglycemia. Nutrition Reviews. 2006;64:331-337.
3. Basch E, Gabardi S, Ulbricht C. Bitter melon (*Momordica charantia*): A review of efficacy and safety. American Journal of Health- System Pharmacy. 2003;60:356-359.
4. Scartezzini P, Speroni E. Review on some plants of Indian traditional medicine with antioxidant activity. J. Ethnopharmacol. 2000;71:23-43. doi: 10.1016/ S0378-8741(00)00213-0
5. Morgan W, Midmore D. Bitter melon in Australia. Australia: Rural Industries Research and Development Corporation; c2002. p. 1-29.
6. Paul A, Mitter K, Sen, Raychaudhuri S. Effect of polyamines in *in vitro* somatic embryogenesis in *Momordica charantia* L. Plant Cell Tissue Organ Culture. 2009;97:303-311.
7. Tan HF, Gan CY. Polysaccharide with antioxidant, α-amylase inhibitory and ACE inhibitory activities from *Momordica charantia*. International Journal of Biological Macromolecules. 2016;85:487-496.
8. Li W, Lin Z, Yang C, Wang Y, Qiao Y. Study on the chemical constituents of *Momordica charantia* L. leaves and method for their quantitative determination. Biomedical Research. 2015;26(3):415-419.
9. Perumal V, Khatib A, Ahmed QU, Uzir B, Abas, Murugesu S, Saiman BMZ, *et al*. Antioxidants profile of *Momordica charantia* fruit extract analyzed using LC-MS-QTOF-based metabolomics. Food Chemistry: Molecular Sciences. 2021;2:100-102.
10. Chokki M, Cudălbeanu M, Zongo C, Dah-Nouvlessounon D, Ghine IO, Furdui B, *et al*. Exploring antioxidant and enzymes (A-amylase and B-Glucosidase) inhibitory activity of *Morinda lucida* and *Momordica charantia* leaves from Benin. 2020;9(4):434-440.
11. Jiang S, Xu L, Xu Y, Guo Y, Wei L, Li X, et al. Antidiabetic effect of *Momordica charantia* saponins in rats induced by high-fat diet combined with STZ. Electronic Journal of Biotechnology. 2020;43:41-47.
12. Perez JL, Jayaprakasha GK, Patil BS. Metabolite profiling and *in vitro* biological activities of two commercial bitter melon (*Momordica charantia* Linn.) cultivars. Food Chemistry. 2019;288:178-186.

13. Gupta C, Khusro A, Salem AZ. Susceptibility of poultry associated bacterial pathogens to *Momordica charantia* fruits and evaluation of *in vitro* biological properties. Microbial pathogenesis. 2019;132:222-229.
14. Chanda J, Mukherjee PK, Biswas R, Malakar D, Pillai M. Study of pancreatic lipase inhibition kinetics and LC-QTOF-MS-based identification of bioactive constituents of *Momordica charantia* fruits. Biomedical Chromatography. 2019;33(4):44-63.
15. Biswas SK. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxidative Medicine and Cellular Longevity Microbial Pathogenesis. 2016;129:124-131.
16. Chao CY, Sung PJ, Wang WH, Kuo YH. Anti-Inflammatory effect of *Momordica charantia* in sepsis mice. Molecules. 2014;19:12777-12788.
17. Shivanagoudra SR, Perera WH, Perez JL, Athrey G, Sun Y, Jayaprakasha GK, *et al*. Cucurbitane-type compounds from *Momordica charantia*: Isolation, *in vitro* antidiabetic, anti-inflammatory activities and in silico modeling approaches. Bioorganic Chemistry. 2019;87:31-42.
18. Liao PY, Lo HY, Liu IC, Lo LC, Hsiang CY, Ho TY. A gastro-resistant peptide from *Momordica charantia* improves diabetic nephropathy in db/db mice via its novel reno-protective and anti-inflammatory activities. Food & Function. 2022,13(4):22-33.
19. Lii CK, Chen HW, Yun WT, Li KL. Suppressive effects of wild bitter gourd (*Momordica charantia* Linn. var. Abbreviata ser.) fruit extracts on inflammatory responses in RAW 264. 7 macrophages. Journal of Ethnopharmacology. 2009;122(2):227-233.
20. Padmashree A, Sharma GK, Semwal AD, Bawa AS. Studies on the antioxygenic activity of bitter gourd (*Momordica charantia*) and its fractions using various *in vitro* models. Journal of the Science of Food and Agriculture. 2011;91(4):776-782.
21. Yang WS, Yang E, Kim MJ, Jeong D, Yoon DH, Sung GH. *Momordica charantia* inhibits inflammatory responses in murine macrophages via suppression of TAK1. Chinese Journal of Natural Medicines. 2018;16(1):72-81.
22. Bai Y, Liu Y, Jia L, Jiang H, Ji M, LVN Huang K, *et al*. Severe acute pancreatitis in China: etiology and mortality on patients. 2007;35(3):232-237.
23. Yang WS, Yang E, Kim MJ, Jeong D, Yoon DH, Sung G H. *Momordica charantia* inhibits inflammatory responses in murine macrophages via suppression of TAK1. Chinese Journal of Natural Medicines. 2018;16(1):72-81.
24. Kim KB, Lee S, Kang I, Kim JH. *Momordica charantia* ethanol extract attenuates H_2O_2-induced cell death by its antioxidant and anti-apoptotic properties in human neuroblastoma SK-N-MC cells. Nutrients. 2018;10(10):1-17.
25. Malekshahi H, Bahrami G, Miraghaee S, Ahmadi SA, Soraya S, Hatami R, *et al*. *Momordica charantia* reverses type II diabetes in rat. Journal of Food Biochemistry. 2019;43(11):131-143.
26. Adelusi TI, Abdul HM, Idris MO, Kehinde OQ, Boyenle ID, Divine UC, *et al*. Exploring the inhibitory potentials of *Momordica charantia* bioactive compounds against Keap1-Kelch protein using computational approaches. In Silico Pharmacology. 2021;9(1):1-4.
27. Wang S, Li Z, Yang G, Ho CT, Li S. *Momordica charantia*: a popular health-promoting vegetable with multifunctionality. Food & Function. 2017;8(5):49-62.
28. Ciou SY, Hsu CC, Kuo YH, Chao CY. Effect of wild bitter gourd treatment on inflammatory responses in BALB/c mice with sepsis. Bio Medicine. 2014;4(3):1-7.
29. Mukherjee R, Jow L, Noonan D, McDonnell DP. Human and rat peroxisome proliferator activated receptors (PPARs) demonstrate similar tissue distribution but different responsiveness to PPAR activators. The Journal of Steroid Biochemistry and Molecular Biology. 1994;51(3-4):157-166.
30. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. Nature. 1998;391(6662):79-82.
31. Abas R, Othman F, Thent ZC. Protective effect of *Momordica charantia* fruit extract on hyperglycaemia-induced cardiac fibrosis. Oxidative Medicine and Cellular Longevity. 2014;10:12-22.
32. Acar OO, Cetin H, Semiz G, Sen A. Suppression of inflammatory cytokines expression with bitter melon (*Momordica charantia*) in TNBS-instigated ulcerative colitis. Journal of Translational Internal Medicine. 2020;8(3)177-187.
33. Hsu C, Hsieh CL, Kuo YH, Huang CJ. Isolation and identification of cucurbitane-type triterpenoids with partial agonist/antagonist potential for estrogen receptors from *Momordica charantia*. J. Agric. Food Chem. 2011;59:4553-4561.
34. Hsu C, Tsai TH, Li YY, Wu WH, Huang CJm, Sai PJ. Wild bitter melon (*Momordica charantia* Linn. var. Abbreviata Ser.) extract and its bioactive components suppress Propionibacterium acnes-induced inflammation. Food Chem. 2012;135;976-984.
35. Leung L, Birtwhistle R, Kotecha J, Hannah S, Cuthbertson S. Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (Bitter melon): A mini review. Brit. J. Nutr. 2009;102:1703-1708.
36. Hanada T, Yoshimura A. Regulation of cytokine signaling and inflammation. Cytokine Growth Factor Rev. 2002;13:413-421.
37. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. Peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature. 1998;391:79-82.
38. Dwijayanti DR, Okuyama T, Okumura T, Nishizawa M. The anti-inflammatory effects of Indonesian and Japanese bitter melon (*Momordica charantia* L.) fruit extracts on interleukin-1β- treated hepatocytes. Functional Foods in Health and Disease. 2019;9(1):16-33.
39. Xu X, Shan B, Liao CH, Xie JH, Wen PW, Shi JY. Anti-diabetic properties of *Momordica charantia* L. polysaccharide in alloxan-induced diabetic mice. Int. J. Biol. Macromol. 2015;81:538-543.
40. Zhang F, Lin L, Xie J. A mini-review of chemical and biological properties of polysaccharides from *Momordica charantia*. Int. J. Biol. Macromol. 2016;92:246-253.
41. Deng YY, Yi Y, Zhang LF, Zhang RF, Zhang Y, Wei ZC, *et al*. Immunomodulatory activity and partial characterization of polysaccharides from *Momordica charantia*. Molecules. 2014;19:13432-13447.
42. Duan ZZ, Zhou XL, Li YH, Zhang F, Li FY, Su-Hua Q. Protection of *Momordica charantia* polysaccharide against intracerebral hemorrhage-induced brain injury

through JNK3 signaling pathway. J. Recept. Signal Transduct. 2015;35:523-529.
43. Cai Y, Liu M, Wu X, Wang Z, Liang C, Yang Y. Study on the antitumor and immune-stimulating activity of polysaccharide from *Momordica charantia*. Pharm. Clin. Res. 2010;18;131-134.
44. Zhang PP, Liu JF, Wang CL, Ye YT, Xie JH. Study on the antimicrobial activities of the extracts from *Momordica charantia* L. Nat. Prod. Res. 2008;20:721-724.
45. Puri M, Kaur I, Kanwar RK, Gupta RC, Chauhan A, Kanwar JR. Ribosome inactivating proteins (RIPs) from *Momordica charantia* for anti viral therapy. Curr. Mol. Med. 2009;9:1080-1094.
46. Fang EF, Zhang CZY, Wong JH. Shen JY, Li CH, Ng TB. The MAP30 protein from bitter gourd (*Momordica charantia*) seeds promotes apoptosis in liver cancer cells *in vitro* and *in vivo*. Cancer. Lett. 2012;324:66-74.
47. Pu Z, Lu BY, Liu WY, Jin SW. Characterization of the enzymatic mechanism of -momorcharin, a novel ribosome-inactivating protein with lower molecular weight of 11,500 purified from the seeds of bitter gourd (*Momordica charantia*). Biochem. Biophys. Res. Commun. 1996;229:287-294.
48. Meng Y, Liu S, Li J, Meng Y, Zhao X. Preparation of an antitumor and antivirus agent: Chemical modification of _-MMC and MAP30 from *Momordica charantia* L. with covalent conjugation of polyethyelene glycol. Int. J. Nanomed. 2012;7:3133.
49. Leung SO, Yeung HW, Leung KN. The immunosuppressive activities of two abortifacient proteins isolated from the seeds of bitter melon (*Momordica charantia*). Immunopharmarcology. 1997;13:159-171.
50. Jabeen U, Khanum A. Isolation and characterization of potential food preservative peptide from *Momordica charantia* L. Arabian J. Chem. 2017;10;S3982-S3989.
51. Dhar P, Chattopadhyay K, Bhattacharyya D, Roychoudhury A, Biswas A, Ghosh S. Antioxidative effect of conjugated linolenic acid in diabetic and non-diabetic blood: An *in vitro* study. J. Oleo Sci. 2007;56:19-24.
52. Tsuzuki T, Tokuyama Y, Igarashi M, Miyazawa T. Tumor growth suppression by _-eleostearic acid, a linolenic acid isomer with a conjugated triene system, via lipid peroxidation. Carcinogenesis. 2004;25;1417:1425.
53. Suzuki R, Arato S, Noguchi R, Miyashita K, Tachikawa O. Occurrence of conjugated linolenic acid in flesh and seed of bitter gourd. J. Oleo Sci. 2010;50:753-758.
54. Akihisa T, Higo N, Tokuda H, Ukiya M, Akazawa H, Tochigi Y, *et al*. Cucurbitane-type triterpenoids from the fruits of *Momordica charantia* and their cancer chemopreventive effects. J. Nat. Prod. 2007;70:1233-1239.
55. Agrawal RC, Beohar T. Chemopreventive and anticarcinogenic effects of *Momordica charantia* extract. Asian Pac. J. Cancer Prev. 2010;11:371-375.
56. Liu CH, Yen MH, Tsang SF, Gan KH, Hsu HY, Lin CN. Antioxidant triterpenoids from the stems of *Momordica charantia*. Food Chem. 2010;118;751-756.
57. Chou CH, Liao MH, Chen TM, Cheng CH, Anggriani R, Tsai CP, *et al*. Bitter melon triterpenes work as insulin sensitizers and insulin substitutes in insulin-resistant cells. J. Funct. Foods 2015;13:214-224.
58. Hsiao PC, Liaw CC, Hwang SY, Cheng HL, Zhang LJ, Shen CC, *et al*. Antiproliferative and hypoglycemic cucurbitane-type glycosides from the fruits of *Momordica charantia*. J. Agric. Food Chem. 2013;61:2979-2986.
59. Han C, Hui Q, Wang Y. Hypoglycaemic activity of saponin fraction extracted from *Momordica charantia* in PEG/salt aqueous two-phase systems. Nat. Prod. Res. 2008;22:1112-1119.
60. Xia K, Yan F, Ye Y, Tang L. The effect of the total saponin extract from the seeds of *Momordica charantia* L.on anti-virus HSV-I and RSV activity. J. Sichuan Univ. 2007, 1.
61. Chang LY, Tang L, Yan, F, Wang S, Chen F. The Effect of the Total Saponin Extract from the Shoots of *Momordica charantia* L. on Anti-virus HSV-II Activity. J. Sichuan Univ. 2004;3:043.
62. Zhang LY, Wang YT, Geng LJ. Bacteriostatic Activity of Total Saponins from Balsam Pear (*Momordica charantia*) against Staphylococcus aureus. J. Microbiol. 2011;1:012.
63. Patel T, Parmar K, Bhatt Y, Patel Y, Patel NM. Isolation, characterization and antimicrobial activity of charantin from *Momordica charantia* linn. Fruit. Pharm. Clin. Res. 2010;2:629-634.
64. Anila L, Vijayalakshmi NR. Beneficial effects of flavonoids from Sesamum indicum, Emblica officinalis and *Momordica charantia*. Phytother. Res. 2000;14:592-595.
65. Qader SW, Abdulla MA, Chua LS, Najim N, Zain MM, Hamdan S. Antioxidant, total phenolic content and cytotoxicity evaluation of selected Malaysian plants. Molecules. 2011;16:3433-3443.
66. Bajpai, Pande A, Tewari SK, Prakash D. Phenolic contents and antioxidant activity of some food and medicinal plants. Int. J. Food Sci. Nutr. 2005;56:287-291.
67. Lin JY, Tang CY. Determination of total phenolic and flavonoid contents in selected fruits and vegetables, as well as their stimulatory effects on mouse splenocyte proliferation. Food Chem. 2007;101:140-147.
68. Saeed S, Tariq P. Antibacterial activities of Mentha piperita, Pisum sativum and *Momordica charantia*. Pak. J. Bot. 2005;37:997.
69. Begum S, Ahmed M, Siddiqui BS, Khan A, Saify ZS, Arif M. Triterpenes, a sterol and a mnocyclic alcohol from *Momordica charantia*. Phytochemistry. 1997;44:1313-1320.
70. Guevara AP, Lim-Sylianco CY, Dayrit FM, Finch P. Acylglucosyl sterols from *Momordica charantia*. Phytochemistry. 1989;28:1721-1724.
71. Shubha AS, Devaraju SM, Srinivasa V, Kantharaj Y, Ravi CS, Akshay A, Shanwaz A. Medicinal and nutritional importance of bitter melon (*Momordica charantia* L): A review article. Journal of Pharmacognosy and Phytochemistry. 2018, 297-300.
72. Ullah M, Chy FK, Sarkar SK, Islam MK, Nurul A. Nutrient and phytochemical analysis of four varieties of bitter gourd (*Momordica charantia*) grown in Chittagong hill tracts, Bangladesh. Asian Journal of Agricultural Research. 2011;5(3):186-193.
73. Ingle A, Kapgate R. Phytochemical screening and anti-microbial activity of *Momordica charantia* Linn. International Journal of Pharmacological Research. 2018;8(7):63-65.3312.

74. Ummi R, Teti E, Endang S. Bioactive compound and nutritious characteristic of bitter melon fruit (*Momordica charantia* L.). Russian Journal of Agricultural and Socio-Economic Sciences. 2018;79(7):308-316.
75. Kim HY, Mok SY, Kwon SH, Lee DG, Cho EJ, Lee S. Phytochemical constituents of bitter melon (*Momordica charantia*). Natural Product Sciences. 2013;19(4):286-289
76. Lovén J, Orlando DA, Sigova AA, Lin CY, Rahl PB, Burge CB. Revisiting global gene expression analysis. Cell. 2012;151(3):476-482.
77. Hu TH, Huang CC, Lin PR, Chang HW, Ger LP, Lin YW, *et al*. Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEP1 in hepatocellular carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2003;15;97(8):1929-1940.
78. Sarwar S, Babur W, Mahwish S, Anwar I. Prevalence of depression among Hepatitis-C patients in tertiary care hospital. Pak J Surg. 2018;34(2):140-143.