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Gastrointestinal symptom and stress recall survey in frontline healthcare workers after consumption of a combined quebracho/conker tree/*M. balsamea willd* extract during the COVID-19 pandemic

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Abstract

Background. Psychological stress induces gastrointestinal (GI) symptoms such as bloating, constipation, abdominal pain/discomfort and diarrhea sometimes of unknown etiology which impairs quality-of-life (QoL) in affected individuals. After a year of the COVID-19 pandemic, the stress impact on healthcare workers is becoming apparent.

Methods. Thirty-five (35) frontline healthcare workers were surveyed by recall regarding previous GI symptoms, their frequency and whether a combined extract of quebracho, conker tree and *M. balsamea Willd* (ATRANTIL®) improved symptomatology, QoL, anxiety and gave them more confidence during the COVID-19 pandemic.

Results. Twenty-eight (28) of 35 participants reported GI distress prior to taking the product with 27 having frequent bloating, abdominal discomfort/pain and constipation as their primary symptoms. After taking the combined extract, 77% reported improvement in bloating followed by constipation (44%), abdominal pain/discomfort (44%), abdominal distention (38%) and diarrhea (5%). Almost 90% stated improved QoL with reductions in anxiety and increased confidence during the pandemic. There were no adverse events during or after taking the supplement.

Conclusion. The combined extract of quebracho, conker tree and *M. balsamea Willd* may improve psychological stress-related GI distress, particularly bloating and overall QoL. More attention should be given to frontline healthcare workers under stress-induced somatization with GI involvement and strategies to manage symptomology.

Introduction

Since the coronavirus (SARS-CoV-2) pandemic began, frontline workers in general face the stress of uncertainty and fear in encountering infected individuals in the wider public. Frontline healthcare workers are at particular risk for increasing stress levels when treating and caring for COVID-19 patients. These healthcare professionals experience anxiety, psychological pressure and post-traumatic stress with their associated workloads [1-3]. Post-traumatic stress accompanying the COVID-19 outbreak in healthcare workers also elicits hyperarousal and decreased sleep quality [4]. Post-traumatic stress is known to induce somatization with gastrointestinal (GI) symptoms [5].

For decades, the brain-gut axis has been implicated in disorders of abdominal pain and motility in the GI tract [6]. More recently, researchers and clinicians have shown that there is an interplay between diet, the microbiome and psychological stress on function of the endocrine and nervous systems with regard to digestive distress in functional GI disorders or more recently described as disorders of gut-brain interaction (DGBI) [7]. Irritable bowel syndrome (IBS) and functional dyspepsia are both DGBIs which can be triggered and exacerbated by psychological stress and anxiety [8,9]. The multiple factors involved in symptomatology of DGBI have greatly influenced the treatment of these disorders with numerous agents that directly impact the microbiome (i.e., antibiotics, probiotics), stress (i.e., neuromodulatory agents), motility (i.e., peripheral opioid receptor agonists/antagonists) as well as complementary alternative medicine approaches that focus on the brain-gut connection (i.e., dietary modification, dietary supplements, acupuncture, etc) [7,10-12].

Though stress can induce symptoms in patients with diagnosed DGBI, it can also more widely impact GI function in healthy populations confronted with extreme circumstances. Taylor *et al.* [13] recently described the stress and anxiety associated with COVID-19 in over 6,800 US and Canadian adults as the COVID Stress Syndrome finding that stress and anxiety had increased substantially and contributed to pre-existing psychopathologies. A recent study of over 2,000 United Kingdom citizens found that fatigue and GI symptoms were the most

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predominant somatic effects of the anxiety during the pandemic [14]. Different surveys of healthcare professionals have found that the stress and anxiety can also contribute to GI symptoms. Nurses and nursing students, for example, reported significant increases in symptoms associated with DGBI [15,16]. And in a recent survey of Italian healthcare workers (N=1,153) assessing the effects of the COVID-19 pandemic on psycho-somatic symptoms, Barello *et al.* [17] found that 37% experienced GI symptomatology.

A marketed dietary supplement containing a blended extract of quebracho, conker tree and *M. balsamea Willd* (ATRANTIL®) has been shown previously to improve bloating, abdominal pain/discomfort and constipation [18,19]. With the psychological stress of frontline healthcare workers in mind during the pandemic, ATRANTIL® was provided to a group of US healthcare professionals and the effect of the dietary supplement on GI symptoms, overall quality of life, anxiety and confidence assessed with an online recall survey.

Materials and methods

Survey design and participants. This was an open-label, non-controlled Healthcare Professional survey conducted using SurveyMonkey® in and around the Dallas-Fort Worth, TX metropolitan area. Thirty-five (35) frontline healthcare professionals participated in the survey. Survey participants were provided with a 30-day supply of an over-the-counter dietary supplement and then asked to answer survey questions. Survey responses represent their recollection prior to and after taking the product. Product consumption and survey participation occurred between June 1, 2020 to August 11, 2020 during the second peak of the coronavirus pandemic in the United States. This survey was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was exempt from IRB review. Consent was obtained from all participants for the use of survey data.

Intervention. Participants were asked to take the recommended daily dose of the combined extract containing quebracho, conker Tree and *M. balsamea Willd* (ATRANTIL®, KBS Research LLC, 15660 N. Dallas Parkway, Suite 700, Dallas, TX 75248) for 30 days. There were no restrictions on taking any prescription drugs, over-the-counter products or diet.

Survey questions. Questions used in the survey and descriptor answers were as follows:

1. Did you have bloating or digestive issues (including abdominal discomfort/pain, diarrhea, constipation) prior to taking ATRANTIL®? (Yes/No)
2. If so, how often did you have digestive symptoms? (Never/Rarely/Sometimes/Often/Very Often)
3. If you answered yes to #1, did your symptoms improve while on ATRANTIL®? (Yes/No)
4. If you had symptoms improve while on ATRANTIL®, what symptoms improved (check all that apply)? (Bloating/Diarrhea/Constipation/Abdominal Distention/Abdominal Pain and/or Discomfort)
5. Did your Quality of Life improve while on ATRANTIL® (including digestive issues, anxiety, overall health, etc.)? (Not at all/Slightly Improved/Moderately Improved/Greatly Improved/Completed Improved)
6. Were you exposed to COVID-19 during the time you were on ATRANTIL®? (Yes/No)
7. Knowing that a healthy gut leads to a healthy immune system, did you have more confidence taking care of your patients while taking ATRANTIL? (Not at All/Slightly More Confident/Moderately More Confident/A Great Deal of Confidence/Completely Confident)

Statistical analysis. Data was accumulated and the percentage of patients responding with descriptor answers described above were tallied for each survey question.

Results

All participants worked in clinical settings as critical, essential frontline workers. Six (6) of 35 participants (17%) confirmed a previous diagnosis of IBS. Nine (9) of 35 participants (26%) were in close contact with COVID-19 patients but did not get infected. The majority of survey participants were from gastroenterology practices. The specific roles of each survey participants in the healthcare system are listed in Table 1.

Participation in this survey occurred between June 1, 2020 to August 11, 2020 during the peak of the first wave in positive SARs-CoV-2 case infections in Texas and the second peak of the coronavirus pandemic in the United States. A total of 35 participants (26 females, 5 males and 4 unknown) consumed product and answered the survey questions. Participant responses to the survey questions with the descriptor answers are shown in Table 2.

The majority of participants (80%) reported GI symptoms prior to taking the blended extract (i.e., bloating, abdominal discomfort and/or pain, diarrhea, constipation) with 77% percent experiencing these symptoms sometimes to very often. The primary symptoms that improved after taking the dietary supplement in participants were bloating (76%), constipation (44%), abdominal distention (38%) and abdominal pain/discomfort (44%). Overall, 89% of participants reported a moderate to complete improvement in quality of life (i.e., less anxiety, overall better health, fewer digestive issues) after taking the product. Knowing that a healthy gut is important for a healthy immune system, 89% felt that taking the product gave them moderately more to complete confidence. Finally, 91% (31/34) reported overall improvement in GI symptoms while on the combined extract.

There were no adverse events to the intervention reported over the course of consumption of the product or after while responding to survey questions.

Discussion

Quebracho extract contains tannins, large delocalized flavonoid structures found in wine [20]. Tannins act to disrupt bacterial lipid bilayers and bind excess hydrogen and methane [21,22], impacting the microbiome by a reduction in gas-producing microbes in the gut and

Table 1. Roles of frontline healthcare worker

Healthcare Professional Role	Participants (n)
Endoscopy Nurse	13
Endoscopy Technician	8
Unknown	4
Acute Care Nurse	3
Physician	2
Medical Assistant	2
Certified Registered Nurse Anesthetist	1
Endoscopy Check In Office Staff	1
Oncology Nurse	1
Total	**35**

Table 2. Frontline healthcare worker survey questions with descriptor responses

Survey Question	Descriptor Response [n (%)]				
Did you have bloating or digestive issues (including abdominal discomfort/ pain, diarrhea, constipation) prior to taking ATRANTIL®?	Yes 28 (80)			No 7 (20)	
If so, how often did you have digestive symptoms?	Never 2 (6)	Rarely 6 (17)	Sometimes 15 (43)	Often 7 (20)	Very Often 5 (14)
If you answered yes to #1, did your symptoms improve while on ATRANTIL®? *	Yes 31 (91)			No 3 (9)	
If you had symptoms improve while on ATRANTIL®, what symptoms improved? *	Bloating 26 (76)	Diarrhea 5 (15)	Constipation 15 (44)	Abdominal Distention 13 (38)	Abdominal Pain/ Discomfort 15 (44)
Did your Quality of Life improve while on ATRANTIL® (including digestive issues, anxiety, overall health, etc.)?	Not at all 0 (0)	Slightly Improved 4 (11)	Moderately Improved 7 (20)	Greatly Improved 14 (40)	Completed Improved 10 (29)
Were you exposed to COVID-19 during the time you were on ATRANTIL®?	Yes 9 (26)			No 26 (74)	
Knowing that a healthy gut leads to a healthy immune system, did you have more confidence taking care of your patients while taking ATRANTIL?	Not at All 1 (3)	Slightly More Confident 3 (9)	Moderately More Confident 8 (23)	A Great Deal of Confidence 10 (29)	Completely Confident 13 (37)

* 34 responded out of 35 participants

the bloating caused by these microorganisms [23]. Conker tree extract contains saponins, also known as escins, which act as antimicrobial agents against methane-producing archaebacteria and also promote intestinal motility [23-25]. Finally, *M. balsamea Willd* extract contains peppermint oil which has been shown to act as an analgesic and antispasmodic in the gut to reduce abdominal pain/discomfort [26]. This combination extract improves symptoms associated with IBS with constipation (IBS-C); bloating, abdominal pain/discomfort and constipation [18,19].

In addition to the antibacterial activity of polyphenolic compounds of saponins and tannins, the molecules also possess potent antioxidant, anti-inflammatory and antiviral activities [27,28]. Escins, or saponins, have a glucocorticoid-like activity and down-regulate nuclear factor κ-light-chain-enhancer of activated B cells (NFκB) p65 subunit expression, a key transcription factor involved in gene expression of inflammatory cytokines [29]. In a mouse model of indomethacin-induced ulceration, escin's antioxidant and anti-inflammatory action alters catalase, glutathione peroxidase and superoxide dismutase activities as well as significantly reduces TNF-α, P-selectin, vascular cell adhesion molecule 1 (VCAM-1), malondialdehyde and myeloperoxidase activity, respectively, in gastric tissue [30]. Tannins not only act as a "sink" for hydrogen and methane in the gut, but also as potent antioxidants. Quebracho tannins are not absorbed in an ovine model, but increase antioxidant capacity of purified hepatic tissue and plasma compared to animals not fed tannins [31].

Reactive oxygen species (ROS) are by-products of normal cellular metabolism but when generated in overabundance due to a pathological condition, they contribute to metabolic diseases. In general, the primary ROS-induced inflammatory pathway involves NFκB activation by TNFα, lipopolysaccharide, thrombin, shear stress within blood vessels, mitochondrial metabolism and dietary factors such as elevated fatty acid and glucose intake [32]. Though endogenous antioxidants in the body respond to ROS challenge, dietary antioxidants, including vitamins C, D and E as well as carotenoids and polyphenols supplement the body's antioxidant capabilities both to reduce the risk for and mitigate damage in cardiovascular disease, chronic obstructive pulmonary disease, inflammatory bowel disease and certain cancers [33]. The highly polymerized quebracho tannins are not highly digestible in the human gut, but bind dietary glucose from starch which helps mitigate elevated blood glucose activation of NFκB-induced inflammation [34]. Colonic microbial digestion of the polymerized tannins leads to a more anti-inflammatory gut microbiome compared to diets with limited polyphenol intake [35]. Finally, a recent *in vitro* model of digestion demonstrates that quebracho tannins [36] yield not only short chain fatty acids (i.e., propanoic and butyric acids) which can support growth of beneficial microbiota, but also the release of anti-inflammatory flavonoids such as epicatechin gallate and gallocatechin that are more readily absorbed into systemic circulation [37]. The antioxidant properties of these and related polyphenols which down-regulate inflammatory pathways in the body may provide some measure of protection against certain diseases and the impact of viral infection.

It has also long been known that polyphenolic compounds improve antioxidant and anti-inflammatory status linked to lower rates of cardiometabolic disorders [28,38] and better outcomes in certain cancers [28,39,40]. In addition, polyphenols also mitigate the effects of certain viral infections [41-43]. Multiple natural compounds and extracts including polyphenols inhibit *in vitro* growth and plaque formation for SARS-CoV and MERS as well as seasonal coronaviruses [44].

The hypoxic phase of the SARS-CoV-2 infection and COVID-19 disease with pneumonia contributes to a ROS-mediated cytokine up-regulation, increased inflammation in endothelial tissue and subsequent coagulation in blood vessels [45-47]. Many different polyphenolic compounds reduce ROS-induced inflammation in respiratory viral infection models of influenza and respiratory syncytial virus [48]. The potential protective effects of polyphenols against respiratory virus-induced ROS-mediated inflammatory disease is intriguing, though studies need to be conducted examining nutritional and oxidative status as a marker for more severe COVID-19 outcomes.

Conclusion

In IBS and inflammatory bowel disease, psychological stress induces permeability of the intestinal epithelium, a contributor to systemic inflammation [49-51]. A small study (N=73) of healthy older adults for self-reported GI symptoms (i.e., diarrhea, constipation, indigestion, abdominal pain, reflux) also demonstrates a link between psychological stress and a release of higher zonulin levels in the plasma, a marker for intestinal permeability [52]. Polyphenols in combination with other natural molecules such as analgesic peppermint provide a way to reduce psychological stress-related GI dysfunction by increasing

the body's antioxidant capacity and relieving GI symptoms while maintaining a healthy gut.

The current survey results in a frontline healthcare worker population suggest that the combined extract of quebracho, conker tree and *M. balsamea Willd* reduces both stress levels in response to the coronavirus pandemic as well as stress-induced GI symptoms to improve their overall quality of life and confidence. Results herein are viewed in the context that the survey is conducted by recall and inaccuracies may exist. A larger, controlled study analyzing specific markers of gut permeability and symptomology is warranted to delineate the exact mechanism by which this dietary supplement improves GI symptoms during elevated periods of psychological stress.

References

1. Park C, Hwang JM, Jo S, Seong Jin B, Joon S, et al. (2020) COVID-19 outbreak and its association with healthcare workers' emotional stress: A cross-sectional study. *J Korean Med Sci* 35: e372. [Crossref]
2. Preti E, Di Mattei V, Perego G, Ferrari F, Mazzetti M, et al. (2020) The psychological impact of epidemic and pandemic outbreaks on healthcare workers: rapid review of the evidence. *Curr Psychiatry Rep* 22: 43. [Crossref]
3. Zhu Z, Xu S, Wang H, Liu Z, Wu J, et al. (2020) COVID-19 in Wuhan: Sociodemographic characteristics and hospital support measures associated with the immediate psychological impact on healthcare workers. *EClinical Medicine* 24: 100443.
4. Yin Q, Sun Z, Liu T, Ni X, Deng X, et al. (2020) Posttraumatic stress symptoms of health care workers during the corona virus disease 2019. *Clin Psychol Psychother* 27: 384-395. [Crossref]
5. Gradus JL, Farkas DK, Svensson E, Ehrenstein V, Lash TL, et al. (2017) Posttraumatic stress disorder and gastrointestinal disorders in the danish population. Epidemiology 28: 354-360. [Crossref]
6. Camilleri M (1990) Disorders of gastrointestinal motility in neurologic diseases. *Mayo Clin Proc* 65: 825-846. [Crossref]
7. Törnblom H, Drossman DA (2018) Psychotropics, antidepressants, and visceral analgesics in functional gastrointestinal disorders. *Curr Gastroenterol Rep* 20: 58. [Crossref]
8. Talley NJ, Holtmann G, Walker MM. Therapeutic strategies for functional dyspepsia and irritable bowel syndrome based on pathophysiology. *J Gastroenterol* 50: 601-613. [Crossref]
9. Talley NJ, Ford AC (2015) Functional dyspepsia. *N Engl J Med* 373: 1853-1863.
10. Dossett ML, Cohen EM, Cohen J (2017) Integrative medicine for gastrointestinal disease. *Prim Care* 44: 265-280. [Crossref]
11. Yoon SL, Grundmann O, Smith KF, Mason SR. Dietary supplement and complementary and alternative medicine use are highly prevalent in patients with gastrointestinal disorders: Results from an online survey. *J Diet Suppl* 16: 635-648. [Crossref]
12. Brenner DM, Sayuk GS (2020) Current US food and drug administration-approved pharmacologic therapies for the treatment of irritable bowel syndrome with diarrhea. *Adv Ther* 37: 83-96. [Crossref]
13. Taylor S, Landry CA, Paluszek MM, Thomas AF, Dean M, et al. COVID stress syndrome: Concept, structure, and correlates. *Depress Anxiety* 37: 706-714. [Crossref]
14. Shevlin M, Nolan E, Owczarek M, McBride O, Jamie M, et al. (2020) COVID-19-related anxiety predicts somatic symptoms in the UK population. *Br J Health Psychol* 25: 875-882. [Crossref]
15. Lee EY, Mun MS, Lee SH, Cho HS (2011) Perceived stress and gastrointestinal symptoms in nursing students in Korea: A cross-sectional survey. *BMC Nurs* 10: 22. [Crossref]
16. Koh SJ, Kim M, Oh DY, Byeong Gwan K, Kook Lae L, et al. (2014) Psychosocial stress in nurses with shift work schedule is associated with functional gastrointestinal disorders. *J Neurogastroenterol Motil* 20: 516-522. [Crossref]
17. Barello S, Palamenghi L, Graffigna G (2020) Burnout and somatic symptoms among frontline healthcare professionals at the peak of the Italian COVID-19 pandemic. *Psychiatry Res* 290: 113129. [Crossref]
18. Brown K, Scott-Hoy B, Jennings LW (2015) Efficacy of a quebracho, conker tree, and *M. balsamea Willd* blended extract in a randomized study in patients with irritable bowel syndrome with constipation. *J Gastroenterol Hepatol Res* 4: 9.
19. Brown K, Scott-Hoy B, Jennings LW (2016) Response of irritable bowel syndrome with constipation patients administered a combined quebracho/conker tree/M. balsamea Willd extract. *World J Gastrointest Pharmacol Ther* 7: 463-468. [Crossref]
20. Bertoldi D, Santato A, Paolini M, Barbero A, Camin F, et al. (2014) Botanical traceability of commercial tannins using the mineral profile and stable isotopes. *J Mass Spectrom* 49: 792-801. [Crossref]
21. Nakayama T, Hashimoto T, Kajiya K, Kumazawa S (2000) Affinity of polyphenols for lipid bilayers. Biofactors 13:147-151. [Crossref]
22. Hook SE, Wright AD, McBride BW (2010) Methanogens: Methane producers of the rumen and mitigation strategies. *Archaea* 2010: 945785. [Crossref]
23. Díaz Carrasco JM, Cabral C, Redondo LM, et al. (2017) Impact of chestnut and quebracho tannins on rumen microbiota of bovines. *Biomed Res Int* 2017: 9610810.
24. Fu F, Hou Y, Jiang W, Ronghua W, Liu K, et al. (2005) Escin: Inhibiting inflammation and promoting gastrointestinal transit to attenuate formation of postoperative adhesions. *World J Surg* 29: 1614-1620. [Crossref]
25. Guo YQ, Liu JX, Lu Y, Denman SE, McSweeney CS, et al. (2008) Effect of tea saponin on methanogenesis, microbial community structure and expression of mcrA gene, in cultures of rumen micro-organisms. *Lett Appl Microbiol* 47: 421-426. [Crossref]
26. Ford AC, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, et al. (2014) Task force on the management of functional bowel disorders. American college of gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 109 Suppl 1: S2-26; quiz S27. [Crossref]
27. Naithani R, Huma LC, Holland LE, Shukla D, McCormick DL, et al. (2008) Antiviral activity of phytochemicals: a comprehensive review. *Mini Rev Med Chem* 8: 1106-1133. [Crossref]
28. Yahfoufi N, Alsadi N, Jambi M, Matar C (2018) The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients* 10: 1618. [Crossref]
29. Wang H, Zhang L, Jiang N, Zhenhua W, Yating C, et al. (2013) Anti-inflammatory effects of escin are correlated with the glucocorticoid receptor/NF-κB signaling pathway, but not the COX/PGF2α signaling pathway. *Exp Ther Med* 6: 419-422. [Crossref]
30. Wang T, Zhao S, Wang Y, Yang Y, Yao L, et al. (2014) Protective effects of escin against indomethacin-induced gastric ulcer in mice. *Toxicol Mech Methods* 24: 560-566. [Crossref]
31. López-Andrés P, Luciano G, Vasta V, Trevor MG, Luisa B, et al. (2013) Dietary quebracho tannins are not absorbed, but increase the antioxidant capacity of liver and plasma in sheep. *Br J Nutr* 110: 632-639. [Crossref]
32. Forrester SJ, Kikuchi DS, Hernandes MS, Qian X, Kathy KG (2018) Reactive oxygen species in metabolic and inflammatory signaling. *Circ Res* 122: 877-902.
33. Liu Z, Ren Z, Zhang J, Chia-Chen C, Eswar K, et al. (2018) Role of ROS and nutritional antioxidants in human diseases. *Front Physiol* 9: 477. [Crossref]
34. Amoako D, Awika JM (2016) Polyphenol interaction with food carbohydrates and consequences on availability of dietary glucose. *Curr Opinion Food Sci* 8: 14-18.
35. Thumann TA, Pferschy-Wenzig EM, Moissl-Eichinger C, Bauer R (2019) The role of gut microbiota for the activity of medicinal plants traditionally used in the European Union for gastrointestinal disorders. *J Ethnopharmacol* 245: 112153. [Crossref]
36. Molino S, Fernández-Miyakawa M, Giovando S, Rufián-Henares JA (2018) Study of antioxidant capacity and metabolization of quebracho and chestnut tannins through *in vitro* gastrointestinal digestion-fermentation. *J Functional Foods* 49: 188-195.
37. Kürbitz C, Heise D, Redmer T, Freya G, Alexander A, et al. (2011) Epicatechin gallate and catechin gallate are superior to epigallocatechin gallate in growth suppression and anti-inflammatory activities in pancreatic tumor cells. *Cancer Sci* 102: 728-734. [Crossref]
38. Soory M (2012) Nutritional antioxidants and their applications in cardiometabolic diseases. *Infect Disord Drug Targets* 12: 388-401. [Crossref]
39. Darvesh AS, Bishayee A (2013) Chemopreventive and therapeutic potential of tea polyphenols in hepatocellular cancer. *Nutr Cancer* 65: 329-344. [Crossref]
40. Losada-Echeberría M, Herranz-López M, Micol V, Barrajón-Catalán E (2017) Polyphenols as promising drugs against main breast cancer signatures. *Antioxidants (Basel)* 6: 88. [Crossref]

41. Andres A, Donovan SM, Kuhlenschmidt MS (2009) Soy isoflavones and virus infections. *J Nutr Biochem* 20: 563-569. [Crossref]

42. Bahramsoltani R, Sodagari HR, Farzaei MH, Amir Hossein A, Maziar G, et al. (2016) The preventive and therapeutic potential of natural polyphenols on influenza. *Expert Rev Anti Infect Ther* 14: 57-80. [Crossref]

43. Furushima D, Ide K, Yamada H (2018) Effect of tea catechins on influenza infection and the common cold with a focus on epidemiological/clinical studies. *Molecules* 23: 1795. [Crossref]

44. Mani JS, Johnson JB, Steel JC, Daniel AB, Paul MN, et al. (2020) Natural product-derived phytochemicals as potential agents against coronaviruses: A review. *Virus Res* 284: 197989. [Crossref]

45. Cecchini R, Cecchini AL (2020) SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. *Med Hypotheses* 143: 110102. [Crossref]

46. Morris G, Bortolasci CC, Puri BK, Lisa O, Wolfgang M, et al. (2020) The pathophysiology of SARS-CoV-2: A suggested model and therapeutic approach. *Life Sci* 258: 118166. [Crossref]

47. Nasi A, McArdle S, Gaudernack G, Westman G, Melief C, et al. (2020) Reactive oxygen species as an initiator of toxic innate immune responses in retort to SARS-CoV-2 in an ageing population, consider N-acetylcysteine as early therapeutic intervention. *Toxicol Rep* 7: 768-771. [Crossref]

48. Khalil A, Tazeddinova D (2020) The upshot of polyphenolic compounds on immunity amid COVID-19 pandemic and other emerging communicable diseases: An appraisal. *Nat Prod Bioprospect* 10: 411-429. [Crossref]

49. Deiteren A, de Wit A, van der Linden L, De Man JG, Pelckmans PA, et al. (2016) Irritable bowel syndrome and visceral hypersensitivity: risk factors and pathophysiological mechanisms. *Acta Gastroenterol Belg* 79: 29-38. [Crossref]

50. Bernstein CN (2017) The brain-gut axis and stress in inflammatory bowel disease. *Gastroenterol Clin North Am* 46: 839-846. [Crossref]

51. Oligschlaeger Y, Yadati T, Houben T, Claudia Maria Condello O, Ronit Shiri S, et al. (2019) Inflammatory bowel disease: A stressed "Gut/Feeling". *Cells* 8: 659. [Crossref]

52. Ganda Mall JP, Östlund-Lagerström L, Lindqvist CM, Algilani S, Rasoal D, et al. (2018) Are self-reported gastrointestinal symptoms among older adults associated with increased intestinal permeability and psychological distress? *BMC Geriatr* 18: 75.