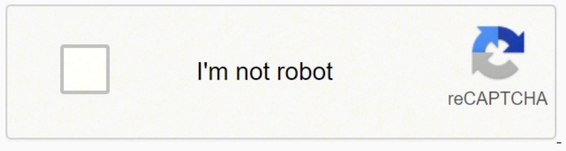

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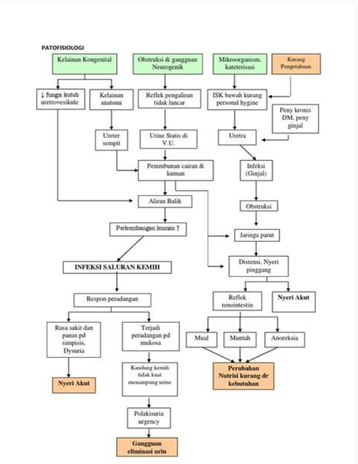
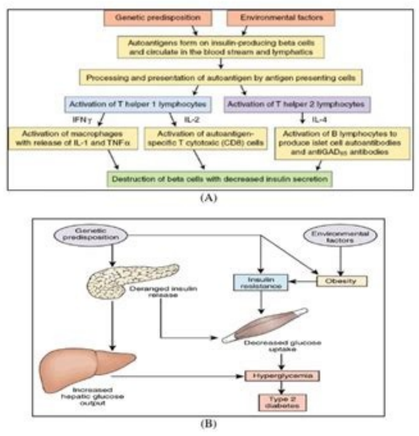


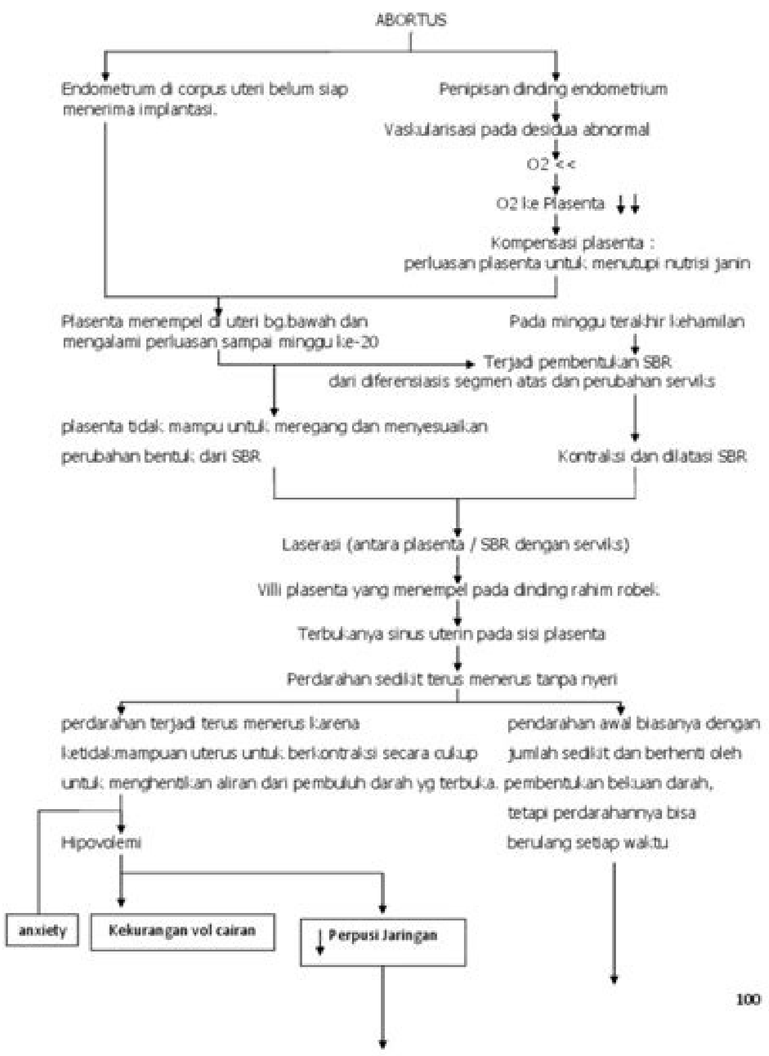
II. Patofisiologi

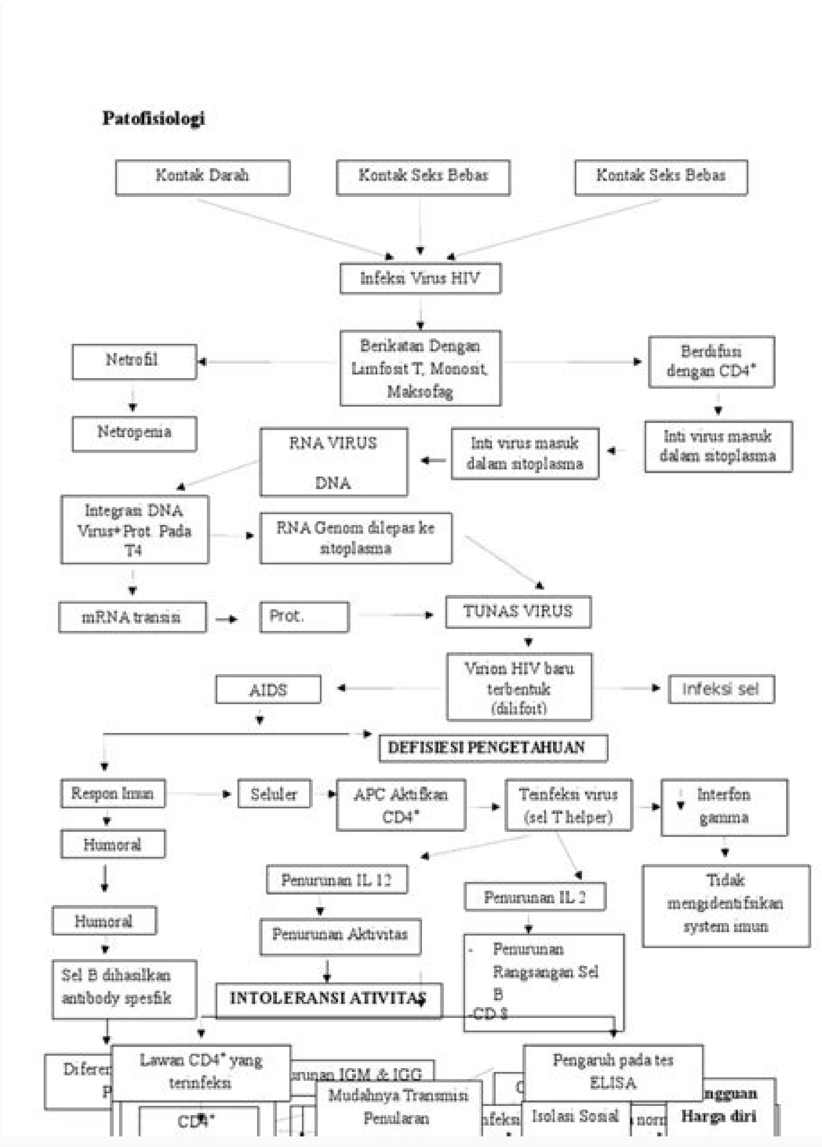
Diabetes mellitus (DM) terbagi menjadi dua tipe, yakni tipe I dan tipe II, dimana sebanyak 10% mengalami DM tipe I dan 90% mengalami DM tipe II.



Gambar 2.2 Patofisiologi Diabetes Mellitus (A) tipe I dan (B) tipe II (McCance & Heuther, 2012; Belleza, 2016)

Berdasarkan gambar, penyakit dikategorikan sebagai DM tipe I apabila disebabkan oleh adanya kerusakan pada sel β pankreas akibat autoimun, sehingga terdapat defisiensi insulin secara mutlak. DM tipe I ini biasanya terjadi pada anak-





Don. Isolation of tiliroside from Spiranthera odoratissima as inhibitor of Trypanosoma cruzi glyceraldehyde-3-phosphate dehydrogenase by using bioactivity-guided fractionation. F. D., Cassels, B. T., and Lim, S. There are in vivo and in vitro studies where the nitroimidazoles induce genotoxic effects, which are related to the ability of cells to reduce these drugs; moreover, the position of the CH_3 and NO_2 groups of these compounds are involved in DNA damage (Boechat et al., 2015). Isoquercitrin: pharmacology, toxicology, and metabolism. L., and Liu, R. The most studied are kaempferol, (–)-epicatechin and tiliroside. dispar. Acta 1820, 1859–1866. R., Vandervijgh, W. [8] Tubuh juga akan memproduksi antibodi terhadap faktor virulensi E. doi: 10.1016/j.foodchem.2016.02.047 PubMed Abstract | CrossRef Full Text | Google Scholar Barbosa, E., Calzada, F., and Campos, R. Synthesis, characterization and antiamoebic activity of chalcones bearing N-substituted ethanamine tail. 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These advances have been a consequence of the various reports on drug resistance in microorganisms as well as the toxicity and side effects of many drugs on humans. M., Agarwal, S. Physiol. (1984). Brain Res. Chemother. Anthocyanidins present the most effective scavenger function, with an activity 10–1,000 times greater than glutathione (GSH) (Cao et al., 1997). 35, S48–S48. Nitroimidazole action in Entamoeba histolytica: a central role for thioredoxin reductase. Lett. In vitro assays showed that their derivatives displayed a better anti-amebic activity than the MTZ reference drug (Leeza Zaidi et al., 2015). Antimicrob. Flavonoid Structure and Classification Flavonoids are natural pigments present in vegetables. 11:e0005832. (2017b). Other compounds with anti-amebic effects are the chalcones. [6,9] Selain membentuk proteksi, respon imun tubuh juga dapat menimbulkan kerusakan jaringan ketika respon yang timbul berlebihan. H., Lai, C. Sci. M., Lares, I., Santiago, P., Herrera, J., et al. Am J Trop Med Hyg 2007; 76:340–4 9. (2013). L., and Comini, M. doi: 10.1016/j.brainresbull.2015.09.002 PubMed Abstract | CrossRef Full Text | Google Scholar Namiduru, E. 44, 223–230. The cysts are secreted in the stool from individuals who harbor E. The expression of REG 1A and REG 1B is increased during acute amebic colitis. R., Pinzón, J. Mode of action of natural and synthetic drugs against Trypanosoma cruzi and their interaction with the mammalian host. doi: 10.4103/0973-1296.204564 PubMed Abstract | CrossRef Full Text | Google Scholar Cao, G., Sofic, E., and Prior, R. doi: 10.1155/2017/2740364 PubMed Abstract | CrossRef Full Text | Google Scholar Bai, Y., Xia, B., Xie, W., Zhou, Y., Xie, J., Li, H., et al. Antiamoebic Activity of Adenophyllum aurantium (L.) strother and its effect on the actin cytoskeleton of Entamoeba histolytica. The differences in the anti-amebic activity of the epicatechin derivatives can be related with the presence of hydroxy groups in the phenolic ring and galloyl moieties [e.g., (–)-epicatechin and (–)-epigallocatechin]. Drug Targets 7, 135–144. Considering all of these remarks, flavonoids can be considered good alternatives for the effective treatment of amebiasis. Antimicrobial effects of Piper hispidum extract, fractions and chalcones against Candida albicans and Staphylococcus aureus. R., Chaur, M. doi: 10.1038/s41598-017-10970-2 PubMed Abstract | CrossRef Full Text | Google Scholar Werner Apt, B. doi: 10.1016/j.bmcl.2015.06.091 PubMed Abstract | CrossRef Full Text | Google Scholar Arias, D. E., Salazar, A. Mutagenic bioassay of certain pharmacological drugs: III. D., Iglesias, A. Commun. L. Immunolocalization and enzymatic functional characterization of the thioredoxin system in Entamoeba histolytica. 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By docking analysis, the authors found that the molecular interaction of kaempferol with the amebic PFOR included nine amino acid residues (Phe 665, Pro 666, Leu 667, Gly 845, Ala 846, Met 851, Tyr 853, Trp 864, and Asn, 866) compared with the four different binding sites of MTZ (Phe 174, His 178, Lys 435, Phe 453, and Tyr 455) (Calzada et al., 2017b). Although there are no reports of a specific target of isoquercetin in the ameba, it is imperative to mention that this flavonoid is metabolized in the bowel and the liver (Valentova et al., 2014); therefore, its administration in in vivo models could diminish the tissue damage induced by E. histolytica, protecting trophozoites from oxidative stress (Choi et al., 2005). Larrea tridentata: a novel source for anti-parasitic agents active against Entamoeba histolytica, Giardia lamblia and Naegleria fowleri. (2010). doi: 10.1021/jf8013074 PubMed Abstract | CrossRef Full Text | Google Scholar Zhu, Q. 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Penempelan atau adherens ini dimediasi melalui molekul lektin Gal/GalNAc yang merupakan salah satu faktor virulensi dari protozoa. brucei gambiense, T. Genotoxic effects of metronidazole. S., Wang, Y. Naringenin prevents experimental liver fibrosis by blocking TGFbeta-Smad3 and JNK-Smad3 pathways. doi: 10.1371/journal.pntd.0005832 PubMed Abstract | CrossRef Full Text | Google Scholar Boechat, N., Carvalho, A. doi: 10.1128/AAC.48.1.69-74.2004 PubMed Abstract | CrossRef Full Text | Google Scholar Pehrson, P., and Bengtsson, E. In P. 33, 255–264. Figure 4. G., Carranza, P. M., Endo, E. Pharmacogn. The most studied flavan-3-ol monomers are (+)-catechins, (–)-epicatechin, (–)-epigallocatechin, (–)-epicatechin gallate, (–)-epigallocatechin gallate, and (+)-gallocatechin (Panche et al., 2016; Borges et al., 2017; Kuhnle, 2017). J Infect Dis 2017; 215:1294–302 7. Sebagai contoh, produksi TNF-α yang tinggi dikaitkan dengan peningkatan kejadian diare akibat E. (1990). 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In addition, it is important to consider the role of these natural molecules that could act directly on trophozoites. E. doi: 10.3164/jcbn.08-211 PubMed Abstract | CrossRef Full Text | Google Scholar Tamayo, E. doi: 10.1016/j.bbrc.2005.05.093 PubMed Abstract | CrossRef Full Text | Google Scholar Mudry, M. It is important to remark that the differences in IC values and the molecular mechanisms of action between kaempferol and its derivatives may be due to the presence of glucosyl moieties on position C3 of the principal structure or the number of hydroxyl groups in ring B, which probably limits the correct activity of tiliroside (Cimanga et al., 2006; Singh et al., 2009) (Table 3). doi: 10.1016/j.jinorgbio.2011.02.009 PubMed Abstract | CrossRef Full Text | Google Scholar Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., et al. Green tea polyphenols as an anti-oxidant and anti-inflammatory agent for cardiovascular protection. 98, 191–193. Cardiovasc. 12, 249–255. histolytica presented a larger amount of this enzyme compared with E. Ethnopharmacol. histolytica can manifest as a commensal or invasive microorganism in the large intestine, producing amebic colitis. [5,10] 4. 12, 70–72. M., et al. Mol. doi: 10.1016/j.jep.2005.01.019 PubMed Abstract | CrossRef Full Text | Google Scholar Calzada, F., Correa-Basurto, J., Barbosa, E., Méndez-Luna, D., and Yepez-Mulia, L. Furthermore, some flavonoids can scavenge O_2^- and others scavenge NO (Hanasaki et al., 1994; Vanacker et al., 1995; Prior and Cao, 2000). The 29-kilodalton thiol-dependent peroxidase of Entamoeba histolytica is a factor involved in pathogenesis and survival of the parasite during oxidative stress. Soc. L., et al. doi: 10.1093/ajcn/74.4.418 PubMed Abstract | CrossRef Full Text | Google Scholar Ondarza, R. (2017). doi: 10.1016/j.molbiopara.2003.10.006 PubMed Abstract | CrossRef Full Text | Google Scholar Alanis, A. Food Chem. The anti-protozoa effect of flavonoids and some of their molecular targets have been demonstrated in Plasmodium falciparum, Trypanosoma brucei brucei, T. The (–)-epicatechin induced morphological changes in the trophozoites at the nuclear and cytoplasmic levels, causing programmed cell death in approximately 95% of amebas (Soto et al., 2010). Based on these results, the authors suggested that resveratrol could be used as alternative treatments for amebiasis (Pais-Morales et al., 2016). I., Mosleh, I. 348, 1565–1573. Genistein and daidzein are the main two soy isoflavones, whose main effects are the inhibition of lipid peroxidation (Lapcík et al., 1998; Yu et al., 2016). In vivo Studies The flavonoids have shown extensive benefits and no side effects in in vivo models of different types of cancer, liver cirrhosis, neurodegenerative diseases and metabolic disorders (e.g., obesity and diabetes) (Goto et al., 2012; Nabavi et al., 2015; Panche et al., 2016; Hernández-Aquino et al., 2017). 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The activity of scavenging O_2^- and NO prevents the formation of $ONOO^-$, which is highly oxidizing. (2017a). However, there are few studies concerning their molecular mechanisms against E. N., and Brumaghim, J. Selain melakukan penempelan sel, trofozoit juga akan mensekresikan modulator sel imun yang akan meningkatkan produksi sitokin dan infiltrasi sel inflamatori.[5] E. The development of novel and effective anti-amebic compounds without side effects is necessary. Biophys. histolytica presents detoxifying enzymes. Treatment of non-invasive amoebiasis. H., Gavrilin, M. Cell Biol. (2006). Due to the low IC_{50}, these flavonoids could be considered good candidates to evaluate their in vivo activity. doi: 10.1016/j.freeradbiomed.2007.02.012 PubMed Abstract | CrossRef Full Text | Google Scholar Arias, D. doi: 10.1016/j.cbpa.2006.03.004 PubMed Abstract | CrossRef Full Text | Google Scholar Mead, J. O., and Ide, T. D., Hughes, M., Houpt, E., and Petri, W. FEMS Microbiol. 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One of the first studies of the anti-amebic activity of kaempferol showed that the purified compound from the aerial parts of Cuphea pinetorum had an inhibitory effect on amebic culture proliferation. Biochem. C., et al. doi: 10.1093/infdis/175.3.734 PubMed Abstract | CrossRef Full Text | Google Scholar Haque, R., Huston, C. L., Leung, T. A., Amer, M. Bioorg. Flavonoids are contained within these natural compounds, which have demonstrated promising results mainly in in vitro studies; however, it is necessary to evaluate their potential activity in in vivo models as a complementary and/or specific therapeutic strategy against E. 52, 673–751. doi: 10.1093/jac/dkn053 PubMed Abstract | CrossRef Full Text | Google Scholar Sharma, S. A. 169, 958–965. Moonah S, Petri W. Entamoeba histolytica-encoded homolog of macrophage migration inhibitory factor contributes to mucosal inflammation during amebic colitis. S., Avecilla, F., Husain, M., and Azam, A. E., Azlan, A., Tang, S. (2005). 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The authors concluded that the enzyme is involved in the detoxification of peroxides and peroxynitrites (Akbar et al., 2004; Sen et al., 2007). They concluded that all these changes modify the pathogenic mechanism, such as adhesion, cytolysis, phagocytosis, and migration (Bolaños et al., 2014, 2015; Calzada et al., 2017a) (Figure 4 and Table 4). New York, NY: Oxford University Press. B. Antiparasitic activity of flavonoids and isoflavones against Cryptosporidium parvum and Encephalitozoon intestinalis. 17, 681–682. falciparum the catechins acts against some identified molecular targets that include enzymes involved in the biosynthesis of fatty acids (FabG, FabZ, FabI, and enoyl-ACP reductase) (Sharma et al., 2007). Flavonoids with anti-amebic activity. Wang, S., Yang, C., Tu, H., Zhou, J., Liu, X., Cheng, Y., et al. The use of plants rich in flavonoids (grapes, cacao and flowers such as Geranium mexicanum) have been shown to exert anti-amebic activity, having cytoskeletal proteins and enzymes related to the glycolytic metabolism of E. Antiprotozoal, Antibacterial and antidiarrheal properties from the flowers of Chiranthodendron pentadactylon and isolated flavonoids. Different chemical modifications may occur in each group, such as hydroxylation, hydrogenation, sulfuration, methylation, acylation, and glycosylation (Andersen and Markham, 2006; Wang et al., 2017). Engl. S., Tarakçioglu, M., Namiduru, M., Kocabaş, R., Erbagci, B., Meram, I., et al. doi: 10.1016/j.bcp.2006.07.039 PubMed Abstract | CrossRef Full Text | Google Scholar Paveto, C., Güida, M. 50, 765–775. In 2015, the Nobel Prize in Medicine was awarded to Professor Youyou Tu for her valuable contributions to the discovery of artemisinin as a natural malaria treatment (Su and Miller, 2015). 186, 343–355. G., Ordoñez Razo, R. Entamoeba histolytica thioredoxin reductase: molecular and functional characterization of its atypical properties. Chem. Free Radic. Green tea catechins potentiate triclosan binding to enoyl-ACP reductase from Plasmodium falciparum (PfENR). Peterson KM, Guo X, Elkahloun AG, et al. Pada infeksi amuba, interferon gamma (IFN-γ) memiliki peran penting dalam memproteksi tubuh. Prostaglandins Leukot. Quercetin, a fluorescent bioflavanoid, inhibits Trypanosoma brucei hexokinase 1. Meth. However, the mechanisms of action and the multiple effects of these natural compounds on the cells are not fully understood. 204, 483–496. Effects of naturally-occurring flavonoids and biflavonoids on epidermal cyclooxygenase and lipoxygenase from guinea-pigs. doi: 10.1016/j.jnutbio.2011.04.001 PubMed Abstract | CrossRef Full Text | Google Scholar Grayer, R. Jr. (1997). 61, 1–21. R., van Acker, F., van der Vijgh, W., and Bast, A. Clín. 61, 1066–1075. However, in symptomatic patients and in invasive disease, the most widely used drugs against E. histolytica pada anak. Free Radicals in Biology and Medicine. This enzyme possesses anti-oxidant properties similar to glutathione and thioredoxin enzymatic systems (Krauth-Siegel and Comini, 2008; Krauth-Siegel and Leroux, 2012). Eukaryotic Cell 6, 664–673. Additional antiprotozoal constituents from Cuphea pinetorum, a plant used in Mayan traditional medicine to treat diarrhoea. In vivo antigiardial activity of three flavonoids isolated of some medicinal plants used in Mexican traditional medicine for the treatment of diarrhea. Table 2. N., Hurtado, G., Iturbe, A., Hernández, E., Tamayo, E., and Woolery, M. Hematol. doi: 10.1016/0165-1218(96)00022-5 PubMed Abstract | CrossRef Full Text | Google Scholar Goto, T., Teraminami, A., Lee, J. 42, 175–181. The correlation between active oxygens scavenging and antioxidative effects of flavonoids. A., Chambers, J. In these studies, it has been observed that the main molecular targets correspond to cytoskeleton related proteins (myosin II heavy chain, α-actinin, and actin). The anti-oxidant function of flavonoids includes the reduction of α-tocopherol, which represents the main anti-oxidant of membranes and low-density lipoproteins (LDL). Pathol. Fitoterapia 94, 55–61. F., Oliva, G., Guido, R. Quercetin induces apoptosis of Trypanosoma brucei gambiense and decreases the proinflammatory response of human macrophages. In this oxidative milieu, the production of O_2^- depends of the activity of the NADPH-oxidase, besides the SOD enzyme converts the superoxide anion to H_2O_2, which activates the myeloperoxidase system (MPO). 76, 611–612. T., Mazur, M., and Telser, J. Biol. Effect of the flavonoids in neutrophils (MPO production), macrophages (decrease of inflammatory mediators), and E. Acta Gen. Braz. The authors demonstrated that the recombinant protein presented thiol peroxidase activity due to its ability to remove H_2O_2. I., Hernández-Carlos, B., Chávez-Munguía, B., Calderón-Oropeza, M. Food Nutr. Haque R, Ali IM, Sack RB, et al. P., Cimanga, K., Van Poel, B., et al. P., Mani, I., Iversen, L., and Ziboh, V. The (–)-epicatechin isoform in in vitro assays has shown the best IC_{50} value of 1.9 µg/ml in inhibiting amebic growth compared with that of other catechin derivatives [e.g., (–)-epigallocatechin, (+)-catechin-3-O-α-L-rhamnopyranoside, and geranins A, B, C, and D] (Meckes et al., 1999; Calzada et al., 2001). F., Siddiqui, S. Promising advances have been made using different secondary metabolites from plant extracts (Procházková et al., 2011; Herrera-Martínez et al., 2016; Bashyal et al., 2017). The trophozoites emerge from the cysts in the intestine, and this vegetative form is able to invade the intestinal mucosa and to disseminate to the liver, producing amebic liver abscess (ALA) (Sehgal et al., 1996; Haque et al., 2003). histolytica (Samarawickrema et al., 1997; Jeelani and Nozaki, 2016). Further studies are necessary to determine the effect of flavonoids in in vivo models to identify their possible molecular targets in amebiasis (Figure 5). Asian Pac. These cells create an oxidative stress environment. 175, 734–736. Agric. PLoS Pathog 2013; 9:e1003489 6. Structural analysis of catechin derivatives as mammalian DNA polymerase inhibitors. Res. doi: 10.1016/j.molbiopara.2005.04.014 PubMed Abstract | CrossRef Full Text | Google Scholar Cimanga, R. 25, 3545–3549. L., Iglesias, A. J Infect Dis 2001; 183:1787–93 10. In vitro IC_{50} of flavonoids against E. doi: 10.1016/j.fitote.2014.01.017 PubMed Abstract | CrossRef Full Text | Google Scholar Khoo, H. Flavonoids and Anti-Oxidant Properties The imbalance between the generation of ROS and reactive nitrogen species (RNS) and their elimination is classically described as “oxidative stress,” which plays an important role in the pathophysiology of many diseases because ROS and RNS can react with lipids, proteins and DNA, inducing their oxidation and causing cell damage. Phytochemistry and pharmacological activities of the genus Prunella. Biomed Res. Nevertheless, it is important to mention that the anti-amebic mechanisms of these flavonoids and their real potential activities have not been determined. Myeloperoxidase binds to and kills Entamoeba histolytica trophozoites. Mex. PubMed Abstract | Google Scholar Valentova, K., Vrba, J., Bancirova, M., Ulrichova, J., and Kren, V. doi: 10.1111/j.1472-8206.1998.tb00951.x PubMed Abstract | CrossRef Full Text | Google Scholar Deponte, M. Apigenin blocks lipopolysaccharide-induced lethality in vivo and proinflammatory cytokines expression by inactivating NF-kappaB through the suppression of p65 phosphorylation. M., Iturbe, A., Hernández, E., Hurtado, G., de Lourdes Gutiérrez, X. A., and Campos-Rodríguez, R. 2017:2740364. M., and Almeida-Amaral, E. In recent years, flavonoids have generated great interest in the scientific community. Infecciones por parásitos más frecuentes y su manejo. D., Canto-Cavalheiro, M. doi: 10.1111/j.1365-3024.2010.01275.x PubMed Abstract | CrossRef Full Text | Google Scholar Pais-Morales, J., Betanzos, A., García-Rivera, G., Chávez-Munguía, B., Shibayama, M., and Orozco, E. Antiprotozoal, antimycobacterial, and anti-inflammatory evaluation of Cnidoscolus chayamansa (Mc Vaugh) extract and the isolated compounds. Flavanones This group is characterized by the lack of a double bond between C-2 and C-3 in the C ring of the flavonoid skeleton. doi: 10.21577/0103-5053.20160315 CrossRef Full Text | Google Scholar Cos, P., Ying, L., Calomme, M., Hu, J. Antibodi terhadap kedua faktor tersebut dinilai berhubungan dengan proteksi terhadap reinfeksi. Mem. G., van Norren, K., and van Leeuwen, P. doi: 10.1042/BA20040006 PubMed Abstract | CrossRef Full Text | Google Scholar Tipoe, G. doi: 10.1016/S0952-3278(98)90125-9 PubMed Abstract | CrossRef Full Text | Google Scholar Krauth-Siegel, R. 214, 755–759. Front. S., Hahn, P., Lyerly, D. Biotechnol. The epigallocatechin was effective in BALB/c mice infected with Leishmania amazonensis. In addition, they present anti-inflammatory effects by inhibiting the activity of lipoxygenase and cyclooxygenase (Kim et al., 1998; Marunaka, 2017). doi: 10.1016/0027-5107(94)90230-5 PubMed Abstract | CrossRef Full Text | Google Scholar Nabavi, S. doi: 10.1021/jm061154d PubMed Abstract | CrossRef Full Text | Google Scholar Soto, J., Gómez, C., Calzada, F., and Ramírez, M. doi: 10.1016/j.biopha.2017.02.021 PubMed Abstract | CrossRef Full Text | Google Scholar Perron, N. Additionally, flavonoids participate as scavengers that can remove these free radicals. In many countries, plant extracts have been employed ancestrally and are a good alternative to treat amebiasis. Furthermore, it is necessary to validate, identify and purify the active compounds with anti-amebic properties before employing them as a treatment. Inorg. A 29 kDa thiol-dependent peroxiredoxin protein (Eh2CysPrx or Eh29) has been reported. Fundam. A., Nandi, N., and Das, P. Disord. K., Kambu, K., Tona, L., Hermans, N., Apers, S., Totté, J., et al. A., Smith, N. The human diet contains between 50 mg and 800 mg of flavonoids per day, depending on the consumption of fruits and vegetables. M., Vikramdeo, K. doi: 10.1016/0891-5849(94)90202-X PubMed Abstract | CrossRef Full Text | Google Scholar Haque, R., Faruque, A. Essent. doi: 10.1080/16546628.2017.1361779 PubMed Abstract | CrossRef Full Text | Google Scholar Kim, H. These results support that this oxidative molecule possesses a central role in the pathophysiological mechanisms underlying amebiasis (Pérez-Fuentes et al., 2000; Namiduru et al., 2011). PubMed Abstract | Google Scholar Middleton, E. doi: 10.1016/S0891-5849(96)00351-6 PubMed Abstract | CrossRef Full Text | Google Scholar Choi, M. Other enzymes inhibited by flavonoids are those involved in the metabolism of arachidonic acid, such as lipoxygenase, cyclooxygenase, microsomal succinoxidase, and NADH oxidase (de Groot and Rauen, 1998). 68, 267–282. PubMed Abstract | Google Scholar Mizushina, Y., Saito, A., Tanaka, A., Nakajima, N., Kuriyama, I., Takemura, M., et al. 1830, 3217–3266. doi: 10.1016/S0887-2333(00)00053-9 PubMed Abstract | CrossRef Full Text | Google Scholar Hernández-Aquino, E., Zarco, N., Casas-Grajales, S., Ramos-Tovar, E., Flores-Beltrán, R. 67, 677–680. Ultrastructural changes on Entamoeba histolytica HM1-IMSS caused by the flavan-3-ol, (-)-epicatechin. Peroxynitrite and peroxiredoxin in the pathogenesis of experimental amebic liver abscess. 48, 924–929. These alterations promote reductions in the invasion to the host tissues, adhesion, proliferation and cell differentiation (Calzada et al., 1998; Mamani-Matsuda et al., 2004; Mead and McNair, 2006; Kerboeuf et al., 2008; Sen et al., 2008; Dodson et al., 2011; Jin et al., 2014; Cornelio et al., 2017) (Figure 2). Because of this, in the last three decades, natural drugs and their products have represented approximately 50% of all treatments that have come to market (Newman and Cragg, 2016), and flavonoids display significant anti-amebic activity in in vitro studies (Figure 3 and Table 3). Flavonoids as antioxidants - determination of radical-scavenging efficiencies. Glutathione catalysis and the reaction mechanisms of glutathione-dependent enzymes. M., and Markham, K. Andersen (Boca Raton, FL: CRC Press), 1003–1071. The MPO caused important damage in trophozoites. This work reported an IC_{50} value near 7.9 µg/ml (Calzada, 2005). Table 3. Flavonoids have low molecular weights (500–4,000 Da) and share a common skeleton of diphenylpyranes (C6-C3-C6) composed of two phenyl rings linked through a ring C of pyran (Figure 1). 44, 112–114. Isoflavonoids The isoflavones are commonly known as ß-glucosides and have a B ring in position 3. Flavones are characterized by a double bond between C-2 and C-3 and a B ring in C-2 (Jiang et al., 2016). Hyg. 105, 745–753. 179, 7121–7127. Immunol. 12, 814–820. The flavone family is a subgroup of flavonoids that is synthesized depending on whether they contain C- or O-glycosylation and a hydroxylated B-ring. histolytica promoting the synthesis and production of pro-inflammatory cytokines and oxidative mediators. Sub. histolytica. The flavonoid (-)-epicatechin affects cytoskeleton proteins and functions in Entamoeba histolytica. PLoS ONE 11:e0146287. histolytica was identified (Ondarza et al., 2005; Tamayo et al., 2005). Flavonoid glycosides isolated from unique legume plant extracts as novel inhibitors of xanthine oxidase. The anti-amebic activity of the MPO was described in in vivo experiments. Moonah SN, Jiang NM, Petri WA Jr. Host immune response to intestinal amebiasis. Biochim. 19, 725–727. Inst. B., Altmann, F., and Duchêne, M. Figure 3. Chalcones The chalcones are referred to as open-chain flavonoids. A., and Yépez-Mulia, L. histolytica interacts with oxidative and non-oxidative metabolites produced by the inflammatory cells. I., van der Hooft, J. This disease produces 100,000 deaths each year, particularly in developing countries. Mycol. These data are comparable with the values of the KI for MTZ (47.64 and 44.01 µM, respectively) (Calzada and Alanis, 2007; Calzada et al., 2017a) (Figure 4 and Table 4). Antiprotozoal constituents from Annona cherimola miller, a plant used in mexican traditional medicine for the treatment of diarrhea and dysentery. Chronic inflammation allows the formation of a granulomatous reaction. In: Scheld W, Whitley R, Marra C, eds. Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships. This group is the main flavonoid responsible for cyanic colors (red, purple, and blue) in vegetables, flowers and fruits. Haque R, Mondal D, Shu J, et al. T., Christensen, K. This enzyme catalyzed the production of hypochlorous acid (HOCl), a highly oxidant molecule, as cytotoxic effector synthetized mainly by neutrophils. doi: 10.2174/138955751503150312141854 PubMed Abstract | CrossRef Full Text | Google Scholar Sehgal, D., Bhattacharya, A., and Bhattacharya, S. Antiobesity effects of anthocyanins in preclinical and clinical studies. According to their structural characteristics (the nature of the C3 element), flavonoids can be classified in Table 2. The field of amebiasis is no exception. A., Sánchez-Monroy, V., and Ramírez-Moreno, E. 48, 69–74. cruzi, Leishmania donovani, Cryptosporidium parvum, Toxoplasma gondii, and Giardia lamblia. The most important anti-oxidant enzymes in mammalian cells are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Valko et al., 2007; Deponte, 2013; Losada-Barreiro and Bravo-Díaz, 2017). 21, 423–432. Metronidazole (MTZ) kills amebas but does not cause damage to cysts. Flavonoids: a review of probable mechanisms of action and potential applications. F., Mello, F. The results showed that the animals treated orally with 30 mg/kg/day of epigallocatechin for 5 days presented a reduction in the size of the ear lesion and a low parasite burden compared with that of the control group (Inacio et al., 2013). doi: 10.1016/j.bbagen.2008.03.006 PubMed Abstract | CrossRef Full Text | Google Scholar Kumar, S., Mishra, A., and Pandey, A. Integr. doi: 10.1016/j.exppara.2010.10.011 PubMed Abstract | CrossRef Full Text | Google Scholar Elizondo, G., Gonsebatt, M. (1994). Melatonin controls oxidative stress and modulates iron, ferritin, and transferrin levels in adriamycin treated rats. G., Regner, E. doi: 10.1002/ptr.1150 PubMed Abstract | CrossRef Full Text | Google Scholar Al-Jaber, H. Involvement of superoxide dismutase and pyruvate:ferredoxin oxidoreductase in mechanisms of metronidazole resistance in Entamoeba histolytica. U., Nakamura, C. Characterization and metabolic diversity of flavonoids in Citrus species. Prensa Med. In vitro 15, 3–6. Entamoeba histolytica: production of nitric oxide and in situ activity of NADPH diaphorase in amebic liver abscess of hamsters. In the case of MTZ, it is known that its biotransformation produces nitroso intermediates (e.g., hydroxy metabolite and acetic acid), which can form adducts in the DNA or inhibit the thioredoxin reductase-generating reactive oxygen species, causing oxidative cell damage (Mudry et al., 1994; Elizondo et al., 1996; Leitsch et al., 2007). Figure 2. histolytica terdiri dari 3 tahapan, yaitu kematian sel pejamu, inflamasi, dan proses invasi. Ralston KS, Solga MD, Mackey-Lawrence NM, et al. Google Scholar Ansari, M. The human body has several anti-oxidant systems, where anti-oxidants are understood as “any substance that retards, prevents or removes oxidative damage to target molecules” (Halliwell and Gutteridge, 2015). doi: 10.1016/j.bbagen.2012.09.018 PubMed Abstract | CrossRef Full Text | Google Scholar Dobbin, C. This enzyme exhibited NADPH dependent oxidase activity, which generates H_2O_2 from O_2. lamblia (IC_{50} 26.6 µg/ml). Flavonoids as peroxynitrite scavengers: the role of the hydroxyl groups. Y., Ohyama, K., Funakoshi, K., Kim, Y. 2014:324230. These compounds have potent anti-oxidant activity. The most common examples are cyanidin, delphinidin, pelargonidin, malvidin, and peonidin (Andersen and Markham, 2006; Azzini et al., 2017). Fatty Acids 58, 17–24. doi: 10.1128/EC.00308-06 PubMed Abstract | CrossRef Full Text | Google Scholar Sen, G., Mukhopadhyay, S., Ray, M., and Biswas, T. These compounds protect organisms against the damage produced by oxidant agents such as UV radiation, pollution, and the chemical substances present in the foods. histolytica, yaitu Gal/GalNAc dan EhMIF. Because of the undesirable effects of MTZ, it is necessary to develop an alternative treatment from biological or synthetic sources that can eliminate E. H., Sajed, D., Poole, L., Hirata, K., Herdman, S., Torian, B. Genistein and daidzein present anti-oxidant activity in peripheral blood lymphocytes, increasing DNA protection against oxidative damage, which contributes to homeostasis in humans (Takahashi et al., 2009). 4th ed. Oswaldo Cruz 110, 492–499. N., Haenen, G. In this study, the authors used histochemistry to determine the presence of the NADPH enzyme that correlated with the size and severity of the lesion. C., and Grayer, R. K. The parasite has two cell cycle stages, the cyst and the trophozoite. In vitro incubation with resveratrol (72 µM) for 48 h induced cell growth arrest, production of ROS, damage to membrane lipids, increased intracellular Ca^{2+}, calpain activation, and decreased superoxide dismutase activity, leading to apoptosis in E. doi: 10.1016/j.molbiopara.2015.11.004 PubMed Abstract | CrossRef Full Text | Google Scholar Bolaños, V., Díaz-Martínez, A., Soto, J., Rodríguez, M. Examples of this group are kaempferol, kaempferol-3-methyl ether, quercetin, and quercetin-3-methyl ether among others. 74, 418–425. Metronidazole (MTZ). 13, 148–152. J., and Bast, A. M., and Abu Zarga, M. Humans obtain these protector flavonoids through direct ingestion of aliments and supplements. In addition, they reported the inhibition of adhesion to Caco-2 cells in amebas co-incubated with kaempferol. histolytica mammalian macrophage migration inhibitory factor). Figure 1. Other important advantages of the use of flavonoids are their anti-oxidant and anti-inflammatory activity, which could participate in the resolution of amebiasis. M., Rosales, J. 87, 49–56. S., Luna-Herrera, J., and Jiménez-Arellanes, M. 28, 512–519. doi: 10.1007/BF02703099 CrossRef Full Text | Google Scholar Sen, A., Chatterjee, N. histolytica trophozoites, as we describe below. histolytica juga menskresikan protein homolog sitokin proinflamatori yang disebut sebagai EhMIF (E. A., Brown, D. Heat shock protein 70 is a potential virulence factor in murine Toxoplasma infection via immunomodulation of host NF-kappa B and nitric oxide. A comparative analysis of genistein and daidzein in affecting lipid metabolism in rat liver. Few infected persons show symptoms with invasion to the bowel or extraintestinal sites, mainly in the liver (Stanley, 2003). R., Paquay, J. 1780, 1236–1248. Z., Gutiérrez-Rebolledo, G. In this milieu, there are a highly oxidative stresses, constituted by NO, peroxynitrites ($ONOO^-$), ROS, and hypochlorous acid. doi: 10.1042/BA20050023 PubMed Abstract | CrossRef Full Text | Google Scholar Othman, A. L., Araujo-Lima, C. The authors suggested that glycosylation on the C-7 position decreased the anti-amebic activity of these flavonoids (Cimanga et al., 2006) (Table 3). D., Carballo, M., Labal de Vinuesa, M., Gonzalez Cid, M., and Larripa, I. PLoS Negl. G., Lujan, H. 23, 768–776. Flavonoids can donate a hydrogen to α-tocopherol radicals and thus protect from oxidation to LDL (Hirano et al., 2001), as observed for quercetin and catechins (Zhu et al., 2000). P. Eur. Cytotoxicity and in vitro susceptibility of Entamoeba histolytica to Morinda morindoides leaf extracts and its isolated constituents. Acacetin has shown important anti-peroxidative and anti-inflammatory activities, and these effects were determined by inhibiting iNOS and COX-2 activity in murine macrophages (Pan et al., 2006) (Table 2). doi: 10.1021/np970237h PubMed Abstract | CrossRef Full Text | Google Scholar Costa, G. (2000). Classification of flavonoids according to structural arrangement. The anti-oxidant activity of flavonoids depends on the redox properties of their phenolic groups (Bors et al., 1990). 109, 552–554. In experimental ALA, NO concentration increases in a time dependent manner, which was found in serum samples from hamsters at different stages of the infection. Closing Remarks In recent years, the use of natural compounds against infectious diseases caused by protozoan parasites has gained popularity among pharmaceutical corporations (Newman and Cragg, 2016). M., Hung, M. 31, S87–S88. A., López-Camarillo, C., Marchat, L. M., and Petri, W. All the authors prepared and edited the figures and tables. J., and Veitch, N. Agents Chemother. Ngobeni R, Abhyankar MM, Jiang NM, et al. Resveratrol induces apoptosis-like death and prevents in vitro and in vivo virulence of Entamoeba histolytica. Flavonoids can regulate inflammation-activating anti-oxidants enzymes (CAT, SOD, and GPx). doi: 10.3390/ijms12129342 PubMed Abstract | CrossRef Full Text | Google Scholar Calleja Bello, M., and Colin Abarranco, M. doi: 10.1016/S0955-2863(99)00065-0 PubMed Abstract | CrossRef Full Text | Google Scholar These anti-oxidants derived from the diet are found in all vegetables and include phenols, phenolic acids, tannins, lignans, and flavonoids (Pizzino et al., 2017). Y., Huang, Y., and Chen, Z. doi: 10.1016/S2221-1691(11)60104-4 PubMed Abstract | CrossRef Full Text | Google Scholar Nicholas, C., Batra, S., Vargo, M. V. They also act as radical scavengers (Tipoe et al., 2007; Bai et al., 2016). Y., et al. doi: 10.1016/j.biocel.2006.07.001 PubMed Abstract | CrossRef Full Text | Google Scholar Vanacker, S. Quercetin interferes with iron metabolism in Leishmania donovani and targets ribonucleotide reductase to exert leishmanicidal activity. doi: 10.1016/j.mycmed.2016.03.002 PubMed Abstract | CrossRef Full Text | Google Scholar de Groot, H., and Rauen, U. histolytica as molecular targets and leading to alterations in DNA replication. G., Nakamura, T. In the case of Toxoplasma gondii, quercetin inhibits the synthesis of HSP90, HSP70, and HSP27, that have been described as virulence factors (Dobbin et al., 2002; Kerboeuf et al., 2008). Flavones present anti-oxidant activities due to their ability to scavenge reactive oxygen species (ROS). Molecules 15, 7363–7377. S., Sen, P., Debnath, A., Pal, A., Bera, T., et al. Andersen (Boca Raton, FL: CRC Press), 918–995. Condes 25, 485–528. W., and Fung, M. doi: 10.1155/2017/8416763 PubMed Abstract | CrossRef Full Text | Google Scholar Prior, R. doi: 10.1016/0035-9203(83)90302-4 PubMed Abstract | CrossRef Full Text | Google Scholar Pérez-Fuentes, R., del Carmen Sánchez-Guillén, M., Velázquez-Rojas, M., Salgado-Rosas, H., Torres-Rasgado, E., and Talamás-Rohana, P. Clin. 305, 127–132. Longev. 40, 833–840. It is important to mention that these anti-oxidant systems maintain a redox balance in the parasite, allowing their survival in adverse oxidative conditions (Arias et al., 2007, 2008). doi: 10.1056/NEJMra022710 PubMed Abstract | CrossRef Full Text | Google Scholar Heijnen, C. doi: 10.3748/wjg.v23.i24.4354 PubMed Abstract | CrossRef Full Text | Google Scholar Herrera-Martínez, M., Hernández-Ramírez, V. Amebic liver abscess. Although the anti-oxidant role of flavonoids is well-documented, many studies have reported their pro-oxidant activity, which seems to depend on their concentration and is directly proportional to the total number of OH groups in the molecule, especially those located in the B ring (Perron et al., 2011). doi: 10.2174/187152907780830905 PubMed Abstract | CrossRef Full Text | Google Scholar Tiwari, K., Kumar, R., and Dubey, V. doi: 10.1093/jac/40.6.833 PubMed Abstract | CrossRef Full Text | Google Scholar Scotti, L., Ferreira, E. Moreover, this natural compound displayed a higher activity than that of MTZ and emetine (Barbosa et al., 2007). Trop. (2017c). Google Scholar Hanasaki, Y., Ogawa, S., and Fukui, S. doi: 10.1055/s-0029-1240599 PubMed Abstract | CrossRef Full Text | Google Scholar Spanou, C., Veskoukis, A. 39, 44–84. Although MTZ is the standard compound for treating amebiasis, it causes adverse effects, such as diarrhea, metallic flavor, loss of appetite, and nausea due to the doses and long-term treatment (1.5 g/day for 10 days) (Haque et al., 1997, 2003; Stanley, 2003). It is important to mention that, until now, there have been no studies of amebiasis using flavonoids in in vivo models. The A and B rings of chalcones are linked by a three-carbon chain instead of a C ring, which is absent (Veitch and Grayer, 2006). Y. (2015). Based on these findings, we strongly suggest that flavonoids could participate as natural anti-oxidant compounds in the highly oxidative environment during ALA, favoring the resolution of liver tissue damage caused not only by the presence of the ameba and its secretion products but also by the inflammatory response characteristic of this pathology. 5:e211. These compounds have anti-oxidant, anti-inflammatory and anti-microbial properties. Gastroenterol. 133, 379–402. doi: 10.1007/s004360000287 PubMed Abstract | CrossRef Full Text | Google Scholar Pacheco-Yepez, J., Jarillo-Luna, R. English grammar editing was done by the American Journal Experts (. 333, 101–109. Aspects Med. The relationships between biological activities and structure of flavan-3-ols. histolytica (myosin II heavy chain, actin and alpha-actinin), affecting adhesion, cytolysis, migration, and phagocytosis (Table 4). Acknowledgments We would like to thank MSc Daniel Coronado-Velázquez for his valuable assistance in the performance of the schematic representations (Figures 4, 5). Biochimie 131, 45–53. With these findings, they concluded that during the establishment of ALA, E. Moreover, in hamsters with ALA, the pre-treatment for 2 or 10 days with 30 mg/kg of resveratrol by oral gavage prevented liver damage by the trophozoites, whereas non-pretreated animals developed extensive ALA (80% of the total liver). Philadelphia, PA: Lippincott Williams & Wilkins; 2014: 770–775 8. D., et al. J., Schroeter, H., and Crozier, A. (2012). S., Salomão, K., Castro, S. Phytother. J., and Ho, C. Figure 5. Acacetin suppressed LPS-induced up-expression of iNOS and COX-2 in murine macrophages and TPA-induced tumor promotion in mice. 133, 187–196. histolytica are the nitroimidazoles (metronidazole and tinidazole) (Marie and Petri, 2013; Ansari et al., 2015). Funding This work was supported by CONACyT grant number 237523 assigned to MS. Enzymol. 2017:8416763. K., Parasuraman, P., Kumar, G., Surolia, N., and Surolia, A. Jr. (2003). A., and Morris, J. 42, 1496–1505. doi: 10.3177/jnsv.47.357 PubMed Abstract | CrossRef Full Text | Google Scholar Inacio, J. The flavonols present important health benefits, such as the anti-oxidant activity, by increasing the activity of catalase and glutathione peroxidase (Bai et al., 2016). I., da Silva, M. Luteolin as an anti-inflammatory and neuroprotective agent: a brief review. 1, 478–481. Protein ini akan menginduksi inflamasi dan meningkatkan produksi matriks metaloproteinase yang akan menghancurkan matriks ekstraseluler pada saluran pencernaan. The specific anti-amebic activity of kaempferol is independent of the plant species [Cnidoscolus chayamansa (Mc Vaugh) and Annona cherimola Miller] (Calzada et al., 2017b; Pérez-González et al., 2017). Another important characteristic is the high nucleophilicity of their A-rings to HO^- and RO^- (Andersen and Markham, 2006; Panche et al., 2016). (A) Natural source of flavonoids with anti-amebic activity, fruits (grapes), seeds (cacao), and flowers (Geranium mexicanum). Tissue injury by reactive oxygen species and the protective effects of flavonoids. (1999). Alteration of DNA replication and apoptosis induction; dysregulation of cytoplasmic proteins: HSP70, PFOR, G/FBPA, and GAPDH; inhibition of cytotoxicity, phagocytosis and alteration of the trophozoite migration (myosin II heavy chain, alpha-actinin, actin, and cortexillin II). A., Gutierrez-Meza, M., Abarca-Rojano, E., Larsen, B. 7:169. (1996). 9, 133–137. The treatment depends on the diagnosis and severity of the illness (Table 1). doi: 10.1371/journal.pone.0146287 PubMed Abstract | CrossRef Full Text | Google Scholar Pan, M. doi: 10.4049/jimmunol.169.2.958 PubMed Abstract | CrossRef Full Text | Google Scholar Dodson, H. doi: 10.1016/j.jep.2006.09.009 PubMed Abstract | CrossRef Full Text | Google Scholar Bashyal, B., Li, L., Bains, T., Debnath, A., and LaBarbera, D. World J. BMC Complement Altern Med. The chemical structure of flavonoids is characterized by the presence of a variable number of phenolic hydroxyl groups (polyphenols). These changes suggest that the ameba lost their virulence factors (Bolaños et al., 2014, 2015) (Figure 4). Leeza Zaidi et al. Flavonoids as scavengers of nitric-oxide radical. 16, 845–850. histolytica trophozoites after 48 h of incubation (IC_{50} 14.7 µg/ml) (Calzada and Alanis, 2007). 56, 8404–8411. Geranins C and D additional new antiprotozoal A-type proanthocyanidins from Geranium niveum. E., and Bast, A. Cell. doi: 10.3389/fphar.2016.00169 PubMed Abstract | CrossRef Full Text | Google Scholar Hirano, R., Sasamoto, W., Matsumoto, A., Itakura, H., Igarashi, O., and Kondo, K. doi: 10.1016/S0039-128X(97)00104-9 PubMed Abstract | CrossRef Full Text | Google Scholar Leeza Zaidi, S., Mittal, S., Rajala, M. Correlation of interferon-gamma production by peripheral blood mononuclear cells with childhood malnutrition and susceptibility to amebiasis. These results are similar to the results for (–)-epicatechin (Bolaños et al., 2014, 2015). In-silico analyses of natural products on Leishmania enzyme targets. Biochemical characterization of dihydroorotase of Leishmania donovani: understanding pyrimidine metabolism through its inhibition. Pharmacognosy Res. S., Akbar, M. Some of the molecular mechanisms triggered by kaempferol in amebas include the dysregulation of actin, myosin II heavy chain, cortexillin II, heat shock protein 70, glyceraldehyde-phosphate dehydrogenase and G/FBPA. Flavanones have anti-oxidant, anti-inflammatory, and neuroprotective activity (Hernández-Aquino et al., 2017). In these conditions, the ameba displays endogenous anti-oxidant enzymes to avoid the effect of these toxic molecules; therefore, E. It is well known that during the establishment of amebiasis in the intestine and in the liver, the inflammatory reaction can promote the participation of pro-inflammatory cytokines. doi: 10.1371/journal.pone.0032214 PubMed Abstract | CrossRef Full Text | Google Scholar Spencer, J., Kuhnle, G., and Rice-Evans, C. M., Upcroft, J. When the amebas were exposed for 1 h to high oxygen concentrations, the expression of eh29 was increased 2.1-fold. histolytica trophozoites. doi: 10.1055/s-2001-17358 PubMed Abstract | CrossRef Full Text | Google Scholar Calzada, F., Cervantes-Martínez, J. 370, 75–80. Other Polyphenol Compounds With Anti-amebic Effects Other flavonoids that have anti-amebic activity are luteolin and apigenin. G., Haenen, G. All authors contributed to manuscript revision, read and approved the submitted version. Am. J. Flavonoids and Their Molecular Targets in Protozoa Flavonoids and their therapeutic applications in human health have been extensively investigated in recent years due to their use in traditional medicine. (2011). 72, 1293–1303. (2007). 13, 240–244. I., et al. A., Tromp, M. 15, 253–269. (2008). D., Meckes, M., Tapia-Contreras, A., and Cedillo-Rivera, R. Increased nitric oxide levels in patients with acute intestinal amebiasis. doi: 10.1016/j.jprot.2014.05.017 PubMed Abstract | CrossRef Full Text | Google Scholar Borges, G., Ottaviani, J. In contrast, other research groups reported that peroxiredoxin was localized in the membrane, and the authors demonstrated that E. Biomed. They also have anti-oxidant and anti-microbial effects (Middleton et al., 2000; Pietta, 2000; Azzini et al., 2017; Khoo et al., 2017). Oxidative stress: harms and benefits for human health. Dengan hancurnya matriks, migrasi sel akan meningkat dan parasit dapat menginvasi pejamu. T. (2003). 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However, flavonoids that chelate Fe^{2+} or Cu^+ can remove a causal factor in the formation of free radicals (e.g., quercetin) (de Groot and Rauen, 1998). For example, luteolin inhibits xanthine oxidase, which is an important enzyme that is involved in ROS production (Cos et al., 1998; Spanou et al., 2012). doi: 10.1006/bbrc.1995.2350 PubMed Abstract | CrossRef Full Text | Google Scholar Veitch, N. Oxidative and Anti-Oxidative Microenvironment in Amebiasis During ALA, E. 89, 89–97. Therefore, (–)-epicatechin can be considered the most promising alternative, safe flavonoid for treatment against amebiasis. doi: 10.1111/j.1574-6968.2006.00263.x PubMed Abstract | CrossRef Full Text | Google Scholar Meckes, M., Calzada, F., Tapia-Contreras, A., and Cedillo-Rivera, R.

Identification of trypanothione from the human pathogen Entamoeba histolytica by mass spectrometry and chemical analysis. More recently, the thioredoxin system (EhTRXR/TRX), a group of anti-oxidant enzymes, has been described in E. Antimicrob Agents Chemother. A., Chatterjee, N. Infections of the Central Nervous System. Prod. Apigenin reduces the phosphorylation of NF-κB/p65 in mouse macrophages and in human monocytes, inhibiting its transcriptional activity and the expression of pro-inflammatory cytokines (Nicholas et al., 2007). Flavonols Flavonols are composed of multiple phenol structural units. In addition, the presence of hydroxy groups in position 3, 4, and 5 in the B ring enhances the anti-oxidant and scavenging activities (Mizushina et al., 2005; Braicu et al., 2011) (Figure 5). “Chalcones, dihydrochalcones, and aurores,” in Flavonoids Chemistry, Biochemistry and Applications, ed Ø. doi: 10.1080/10286020.2010.502892 PubMed Abstract | CrossRef Full Text | Google Scholar Andersen, Ø. 146, 601–620. Int. Table 1. 12, 9342–9353. V., and Dias, B. doi: 10.1016/S0188-4409(00)00179-X PubMed Abstract | CrossRef Full Text Pérez-González, M. (2004). Trypanothione reductase from the human parasite Entamoeba histolytica: a new drug target. Flavan-3-ols (Flavanols) The flavanols or catechins, also referred to as flavan-3-ols, are non-glycosylated compounds that are present in plants in the form of monomers (catechins). A., and Guerrero, S. S., Kerasioti, T., Kontou, M., Angelis, A., Aligiannis, N., et al. Chalcones have nutritional and biological benefits owing to their anti-bacterial and anti-parasitic activities (Nowakowska, 2007; Costa et al., 2016). In particular, tiliroside showed an IC50 of 7.45 μg/ml against E. L., and Cao, G. Based on previous reports, kaempferol, (–)-epicatechin, and (–)-epigallocatechin present different IC50 for anti-amebic activity and presented the best IC50 values that showed good activity against E. However, isoquercitin, a quercetin derivative, inhibited the viability and growth of E. (2009). Usually, in plants, polyphenolic metabolites can be present in roots, leaves, flowers, and fruits. These results showed that this enzyme, which was produced by inflammatory cells, is capable of protecting host tissue against E. [Epub ahead of print]. Nature 2014; 508:526–30 5. M. Planta Med. Protein ini juga dinilai memiliki korelasi positif dengan proses inflamasi pada pasien amebiasis kolitis. Life Sci. 61, 71–76. Identification of isoflavonoids in beer. Studies of genotoxicity and mutagenicity of nitroimidazoles: demystifying this critical relationship with the nitro group. Table 4. doi: 10.4049/jimmunol.179.10.7121 PubMed Abstract | CrossRef Full Text | Google Scholar Nijveldt, R. The efficacy of intragastric treatment with (–)-epicatechin at 0.072 μmol/kg was demonstrated in CD-1 mice infected with G. (B) Possible mechanisms of the flavonoids as direct scavenger of ROS, ONOO−, and NO, enhancer of CAT, SOD, and GPx enzymes and regulation of inflammation via STAT and NF-κB. An unusual surface peroxiredoxin protects invasive Entamoeba histolytica from oxidant attack. The hydroxyl group is bound to position 3 of the C ring, and has no double bonds between positions 2 and 3. Moreover, flavonoids are direct chelators of ONOO−, as was reported for quercetin (Haenen et al., 1997; Heijnen et al., 2001; Spencer et al., 2003). doi: 10.1016/j.biochi.2016.09.009 PubMed Abstract | CrossRef Full Text | Google Scholar Tsutsumi, V., Mena-López, R., Anaya-Velázquez, F., and Martínez Palomo, A. 13:120. doi: 10.1016/0076-6879(90)86128-I PubMed Abstract | CrossRef Full Text | Google Scholar Braicu, C., Pilecki, V., Balacescu, O., Irimie, A., and Neagoe, I. Pharmacother. 23, 4354–4368. We cannot discard that flavonoids act directly with neutrophils and macrophages to kill amebas (Figures 5A,B). The recombinant protein is able to catalyze the reduction of NADPH or NADH and S-nitrosothiols. D., Calzada, F., Cedillo-Rivera, R., and Meckes, M. In general, the anti-oxidant activity of a flavonoid depends on three of its structural characteristics: (a) the presence of the catechol group in the B ring, (b) a Δ2 double bond and a 4-oxo group in the C ring, and (c) the hydroxyl groups on positions C-3 and C-5 (Wolfe and Liu, 2008; Kumar et al., 2013). Plants with anti-amebic activity that have been used as sources of catechins and their derivatives include Helianthemum glomeratum, Osyris alba, Chiranthodendron pentadactylon, Geranium niveum, Geranium mexicanum, and Rubus coriifolius (Meckes et al., 1999; Alanis et al., 2003; Al-Jaber et al., 2010; Calzada et al., 2017c). Haenen, G. treatment with metronidazole by the intravenous route. Free radicals and polyphenols: the redox chemistry of neurodegenerative diseases. (2002). Amebiasis and mucosal IgA antibody against the Entamoeba histolytica adherence lectin in Bangladeshi children. Mini Rev. Boca Raton, FL; London; New York, NY: CRC press; Taylor & Francis. 117, 81–91. 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Thus, it is important to consider the doses of MTZ administration, the individual susceptibility and to evaluate the risk-benefit in relation with the severity of the infection (Mudry et al., 1994; Elizondo et al., 1996). Since the 1990s, medicinal plants have gained popularity as potential therapeutic alternatives. General structure of flavonoids. (1997). Kaempferol derivatives also exhibit considerable anti-amebic activity. The (–)-epicatechin administered 6 days post-infection decreased the number of parasites in the small intestine. The authors also demonstrated a dysregulation of glycolytic enzymes and stress oxidative proteins. A comparison between tinidazole alone and in combination with diloxanide furoate. Author Contributions Authors that contributed to writing the manuscript: MS (introduction and closing remarks), JP-Y and RC-R (flavonoids structure and classification), RJ-L (flavonoids and anti-oxidant properties), NF-H and LC-J (flavonoids and their molecular targets in protozoa), MM-C and PG-T (flavonoids with anti-amebic activity; in vitro and in vivo studies and molecular targets). I., Martino, V., Coussio, J., Flawiá, M. In the initial stages of ALA, the amebas are surrounded by neutrophils and posteriorly by macrophages. PubMed Abstract | CrossRef Full Text | Google Scholar Bors, W., Heller, W., Michel, C., and Saran, M. These activities are modulated by three general mechanisms: (a) scavenging the ROS, (b) suppressing the formation of free radicals by enzymatic inhibition or chelating elements involved in the formation of them, and (c) protecting or upregulating the anti-oxidants. PLoS ONE 7:e32214. Comp. Pharmacological treatment of amebiasis. Med. Patofisiologi Amebiasis general_alomedika 2018-12-17T15:14:11+07:00 2018-12-17T15:14:11+07:00 Patofisiologi amebiasis, dikenal juga sebagai amubiasis, amoebiasis, atau disentri ameba, berkaitan dengan terjadinya infeksi oleh Entamoeba histolytica, transmisi parasit, dan respon imun pejamu. Kaempferol has a high affinity for pyruvate ferredoxin oxidoreductase (PFOR), an important therapeutic target in E. Increased serum nitric oxide and malondialdehyde levels in patients with acute intestinal amebiasis. Proteomics 111, 74–85. Oxid. Metronidazole hydrazone conjugates: design, synthesis, antiamoebic and molecular docking studies. In contrast, there are few reports of flavonoids in parasitic diseases using in vivo models. Chemical constituents of Osyris alba and their antiparasitic activities. Conflict of Interest Statement The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Usually, the drug can attack luminal forms and invasive amebiasis. B., da Silva, M. Flavonoids and their possible targets on E. doi: 10.1016/j.lfs.2008.08.004 PubMed Abstract | CrossRef Full Text | Google Scholar Pacheco-Yépez, J., Campos-Rodríguez, R., Shibayama, M., Ventura-Juárez, J., Serrano-Luna, J., and Tsutsumi, V. 45, 32–39. histolytica is capable of inducing an important inflammatory response, which is mainly composed of neutrophils (PMNs) and macrophages. Kaempferol inhibits Entamoeba histolytica growth by altering cytoskeletal functions. 98, 179–189. G. A., Thammapalerd, N., and Upcroft, P. H. HortScience 35, 588–592. V., et al.

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