In vitro anti-inflammatory activity of *Fragaria* spp. in human gastric epithelial cell

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Strawberries (*Fragaria* spp.) are commonly consumed berries, and are the most popular choice among consumers, being eaten both fresh and frozen, as well as in different processed products such as desserts, juice, nectar, and jam. The nutritional quality of strawberries is correlated to the presence of several compounds, including polyphenols. Among polyphenols, strawberries are a rich source of proanthocyanidins, anthocyanins, flavonoids, and ellagitannins.
The gastrointestinal tract represents an important barrier between the human hosts and microbial populations. One potential consequence of host-microbial interactions is the development of mucosal inflammation, which can lead to gastritis and ulcer. During gastric inflammation, epithelial cells release higher levels of cytokines including IL-1β, TNFα, and IL-8, a potent neutrophil-activating chemokine that plays a central role in gastritis (Crabtree et al., 1995). This response strictly depends on the activation of NF-κB pathway (Yasumoto et al., 1992). Strawberry has been shown to inhibit ethanol-induced gastritis in rats, and the effect was related to the presence of anthocyanins (Alvarez-Suarez et al., 2011). However, the inhibitory effect of tannin-enriched fractions (TEFs) from strawberries against gastric inflammation was not previously described. The aim of the present work was to investigate if tannins from *Fragaria* spp. could contribute to inhibit gastric inflammation. For this purpose, berries were harvested at maturity and the extraction of polyphenols was carried out with a mixture acetone/water (70/30 v/v), as previously reported (Gasperotti et al., 2010). TEFs and the most abundant ellagitannin agrimoniin were assayed to investigate a) the inhibition of NF-kB translocation and driven transcription; b) the effect on IL-8 release in gastric epithelial cell line (AGS) stimulated with TNFα and IL-1ß. Both TEF from *Fragaria* x *ananassa* and *Fragaria vesca* inhibited TNFα-induced NF-κB driven transcription and nuclear translocation. IC_{50} on TNFα-induced NF-κB nuclear translocation were 0.25 and 1.01 μg/ml, respectively. When IL-1β stimulated NF-κB pathway, inhibition by TEFs was lower. Agrimoniin inhibited TNFα-induced NF-κB driven transcription and nuclear translocation in a concentration-dependent manner. When the stimulus was IL-1β, the effect of the pure compound was lower with respect to TNFα-induced NF-κB pathway. Since IL-8 is widely involved in gastric inflammation, and it has been demonstrated that the expression of this chemokine is NF-κB dependent, the following experiments were devoted to evaluate the effect of the extracts/individual compound on IL-8 secretion induced by TNFα and IL-1β in AGS cells. Both the extracts and agrimoniin were able to inhibit IL-8 release, induced by TNFα and IL-1β, in a concentration-dependent way. IC_{50} of *Fragaria* x *ananassa* and *Fragaria vesca* extracts on TNFα-induced IL-8 release were 0.09 and 0.29 μg/ml, respectively. The effect of the extracts on TNFα-induced IL-8 release was ten fold higher than that induced by IL-1β. Agrimoniin inhibited preferentially TNFα-induced IL-8 release as well (IC_{50} 0.042 μM). Our results report that *Fragaria* spp., which are widely consumed as nutrients, show *in vitro* anti-inflammatory effect at the gastric level, being agrimoniin responsible, at least in part, for the biological activity exerted by the extracts. These results confirm our hypothesis that tannins, in addition to anthocyanins, could exert beneficial effect at the gastric level.

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