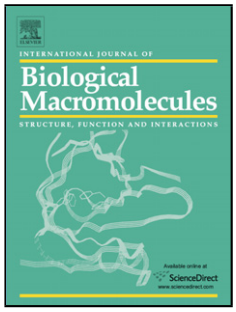

Title: Flavonoids determine the rate of fibrillogenesis and structure of collagen type I fibrils in vitro

Authors: Yuri A. Kim, Yury S. Tarahovsky, Sergei G. Gaidin, Elena A. Yagolnik, Eugeny N. Muzafarov

PII: S0141-8130(17)31385-5
DOI: http://dx.doi.org/doi:10.1016/j.ijbiomac.2017.06.070
Reference: BIOMAC 7750

To appear in: *International Journal of Biological Macromolecules*

Received date: 19-4-2017
Revised date: 13-6-2017
Accepted date: 14-6-2017

Please cite this article as: Yuri A.Kim, Yury S.Tarahovsky, Sergei G.Gaidin, Elena A.Yagolnik, Eugeny N.Muzafarov, Flavonoids determine the rate of fibrillogenesis and structure of collagen type I fibrils in vitro, International Journal of Biological Macromoleculeshttp://dx.doi.org/10.1016/j.ijbiomac.2017.06.070

Flavonoids determine the rate of fibrillogenesis and structure of collagen type I fibrils in vitro

Yuri A. Kim[a], Yury S. Tarahovsky[b], Sergei G. Gaidin[a*], Elena A. Yagolnik[c], Eugeny N. Muzafarov[c]

[a]Institute of Cell Biophysics, RAS, Pushchino, Moscow Region, 142290, Russia

[b]Institute of Theoretical and Experimental Biophysics, RAS, Pushchino, Moscow Region, 142290, Russia

[c]Tula State University, Tula, 300000, Russia

*Corresponding author, Institute of Cell Biophysics, RAS, 142290, Pushchino, Moscow Region, Russia. E-mail address: ser-gajdin@yandex.ru

Highlights

- Flavonoids effect on the process of fibril formation of collagen type I in vitro
- Different flavonoids can accelerate or slow down the formation of fibrils
- The effect correlates with the number of hydroxyls in B-rings of flavonoids
- Molecular modeling suggests the significance of lipophilicity exactly of B-ring

Abstract

Collagen fibrils are produced from collagen monomers not only in vivo, but also in vitro. The ability to have an influence on the structure and properties of fibrils may find medical application and can be useful for controlling the formation of collagen gels and sheets in tissue engineering. Here we investigated the influence of flavonoids, distinguished by the number of hydroxyl groups in the B-ring, on the formation of collagen fibrils. A correlation was found between the number of hydroxyl groups, lipophilicity of molecules and their ability to influence the fibril formation. The molecules with a smaller number of hydroxyls (flavone and kaempferol) were more lipophilic and accelerated the formation of fibrils, whereas molecules with a larger number of hydroxyls (quercetin, myricetin) were more hydrophilic and prevented the fibril formation. Among the studied substances, an exception was taxifolin, which accelerated the formation of fibrils in spite of the increased hydrophilicity of this compound. However, molecular modeling revealed that all investigated accelerators of the fibril formation, including taxifolin, were distinguished by the increased lipophilicity exactly in the B-ring. This suggests a critical role of the B-ring lipophilicity in the ability of the studied flavonoids to accelerate the formation of collagen fibrils.

Keywords: Collagen; fibrils; flavonoids; taxifolin; quercetin; flavone

1. Introduction

Collagen type I is one of the most abundant mammalian proteins which is present in epithelial tissue, cartilages, tendons, muscles, teeth, and walls of blood vessels. The collagen found its wide application as a biomaterial in surgery, tissue engineering, cosmetology [1–3]. It is known that the abnormality in the arrangement of collagen fibrils causes various disorders of connective tissues including osteoporosis [4], scoliosis [5], Ehlers-Danlos syndrome [6], Marfan syndrome etc [7]. In the case of Ehlers-Danlos syndrome, for example, the hyperextensibility of skin correlates with increased diameter of collagen fibrils to 110 – 140 nm compared to normal 90 – 100 nm. Besides, the regular D-periodical packing of molecules is disturbed [8]. Fibrils of variable size and packing are necessary for tissue protection and wound healing [9]. The influence of physical and chemical factors on the assembling process and structure of collagen fibrils have been thoroughly studied [10–14]. Plant polyphenols have long been used to stabilize the collagen-containing biomaterials [15]. During the last years a great attention has been paid to effects of flavonoids on collagen fibril formation [10–14,16–18]. The study of these aspects can be useful in biomedicine [19–22]. The stabilizing effect of flavonoids on a protein is realized through the interaction of hydroxyl groups with serine, hydroxyproline, carboxylic groups of aspartic acid, amino groups of lysine and amide groups of asparagines [18]. As we demonstrated earlier [23], the flavonoid taxifolin may accelerate the formation of collagen fibrils in vitro. Because of this interesting fact it was decided to find other flavonoids which can effect on collagen fibril formation in the same way. In present work we also tried to reveal the relationship between the structure of flavonoids and their ability to change the rate of collagen fibrillogenesis in vitro. In this study the following flavonoids were used: kaempferol, quercetin, and myricetin, which are related to the group of flavonols (IUPAC name of backbone is: 3-hydroxy-2-phenylchromen-4-one), and taxifolin which is related to the group of flavanonols (backbone is: 3-hydroxy-2,3-dihydro-2-phenylchromen-4-one), that distinguishes from the flavonols by the absence of the double bond between carbon atoms 2 and 3. Besides, we used flavone, which has no hydroxyl groups (Fig.1). The mentioned molecules