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Biophysical evidence for differential gallated green tea catechins binding to membrane type-1 matrix metalloproteinase and its interactors

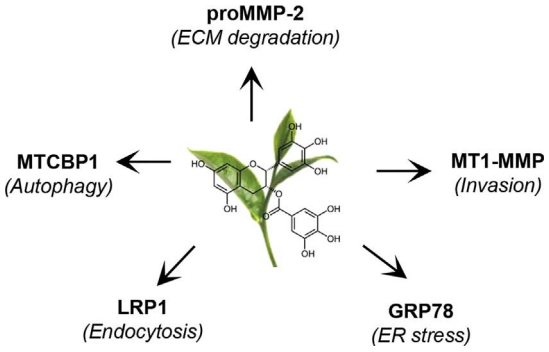
Djahida Djerir[a], Mustapha Iddir[a], Steve Bourgault[b], Sylvie Lamy[a], Borhane Annabi[a,b,*]

[a] Laboratoire d'Oncologie Moléculaire, Centre de recherche BIOMED, Université du Québec à Montréal, Quebec H3C 3P8, Canada
[b] Centre de recherche Pharmaqam, Département de Chimie, Université du Québec à Montréal, Quebec H3C 3P8, Canada

HIGHLIGHTS

- Multiple tumorigenic processes involve membrane type-1 matrix metalloproteinase.
- Disease prevention properties of tea have been attributed to catechins.
- Surface plasmon resonance was used to assess catechins binding to MT1-MMP.
- Gallated catechins have higher affinity towards MT1-MMP and its interactors.

GRAPHICAL ABSTRACT



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ABSTRACT

Membrane type-1 matrix metalloproteinase (MT1-MMP) is a transmembrane MMP which triggers intracellular signaling and regulates extracellular matrix proteolysis, two functions that are critical for tumor-associated angiogenesis and inflammation. While green tea catechins, particularly epigallocatechin gallate (EGCG), are considered very effective in preventing MT1-MMP-mediated functions, lack of structure-function studies and evidence regarding their direct interaction with MT1-MMP-mediated biological activities remain. Here, we assessed the impact in both cellular and biophysical assays of four ungallated catechins along with their gallated counterparts on MT1-MMP-mediated functions and molecular binding partners. Concanavalin-A (ConA) was used to trigger MT1-MMP-mediated proMMP-2 activation, expression of MT1-MMP and of endoplasmic reticulum stress biomarker GRP78 in U87 glioblastoma cells. We found that ConA-mediated MT1-MMP induction was inhibited by EGCG and catechin gallate (CG), that GRP78 induction was inhibited by EGCG, CG, and gallocatechin gallate (GCG), whereas proMMP-2 activation was inhibited by EGCG and GCG. Surface plasmon resonance was used to assess direct interaction between catechins and MT1-MMP interactors. We found that gallated catechins interacted better than their ungallated analogs with MT1-MMP as well as with MT1-MMP binding partners MMP-2, TIMP-2, MTCBP-1 and LRP1-clusterIV. Overall, current structure-function evidence supports a role for the galloyl moiety in both direct and indirect interactions of green tea catechins with MT1-MMP-mediated oncogenic processes.

Abbreviations: C, catechin; CNS, central nervous system; ConA, concanavalin-A; EC, epicatechin; ECM, extracellular matrix; EGC, epigallocatechin; EGCg, epigallocatechin gallate; GBM, glioblastoma; 67LR, 67 k kDa laminin receptor; LRP-1, low-density-lipoprotein receptor-related protein-1; MMP-2, metalloproteinases-2; MT1-MMP, membrane type-1 matrix metalloproteinase; MTCBP-1, MT1-MMP cytoplasmic tail-binding protein-1; SPR, surface plasmon resonance; TIMP-2, tissue inhibitor of metalloproteinase-2; TLR, Toll-like receptor

* Corresponding author at: Laboratoire d'Oncologie Moléculaire, Université du Québec à Montréal, C.P. 8888, Succ. Centre-ville, Montréal, Québec H3C 3P8, Canada.
E-mail address: annabi.borhane@uqam.ca (B. Annabi).

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1. Introduction

The use of various natural phytochemicals and dietary compounds in cancer chemoprevention is believed to prevent the onset of patho-physiological processes which regulate tumor growth [1]. Furthermore, epidemiological and pre-clinical data, obtained through *in vitro* and *in vivo* animal studies, support the concept that these compounds can downregulate oncogenic signaling pathways or sensitize malignant cells to cytotoxic agents [2]. Unfortunately, only a limited number of these compounds have been tested in clinical trials often because of the lack of structure-function molecular evidence supporting their capacity to interact with their cellular targets and to interfere with the associated biological processes [3].

Among natural polyphenolic compounds, prophylactic and therapeutic properties have been attributed to green tea catechins and black tea theaflavins [4]. In fact, among tea polyphenols which possess potent antioxidant and anti-inflammatory properties that modulate signaling pathways [5], epigallocatechin-3-gallate (EGCG) is one of the most studied active substances and considered to act through diversified molecular mechanisms [6]. Its *in vitro* cellular effects were documented in numerous central nervous system (CNS) cancer cell models including glioblastoma [7–9], pediatric brain tumor-derived medulloblastoma [10], and in childhood primitive neuroectodermal brain tumors [11]. Interestingly, combining EGCG with Temozolomide [12] or to ionizing radiation [13, 14] was found to enhance therapeutic efficacy. Among the molecular processes targeted by EGCG, inhibition of cell proliferation, survival, *in vitro* endothelial cell tubulogenesis, pro-inflammatory intracellular transducing events, as well as cell migration/invasion processes have been reported [15, 16]. In addition, EGCG was recently documented to alter the membrane bound matrix metalloproteinase MT1-MMP functions in cancer cell invasion and survival processes through the inhibition of its capacity to hydrolyze extracellular matrix

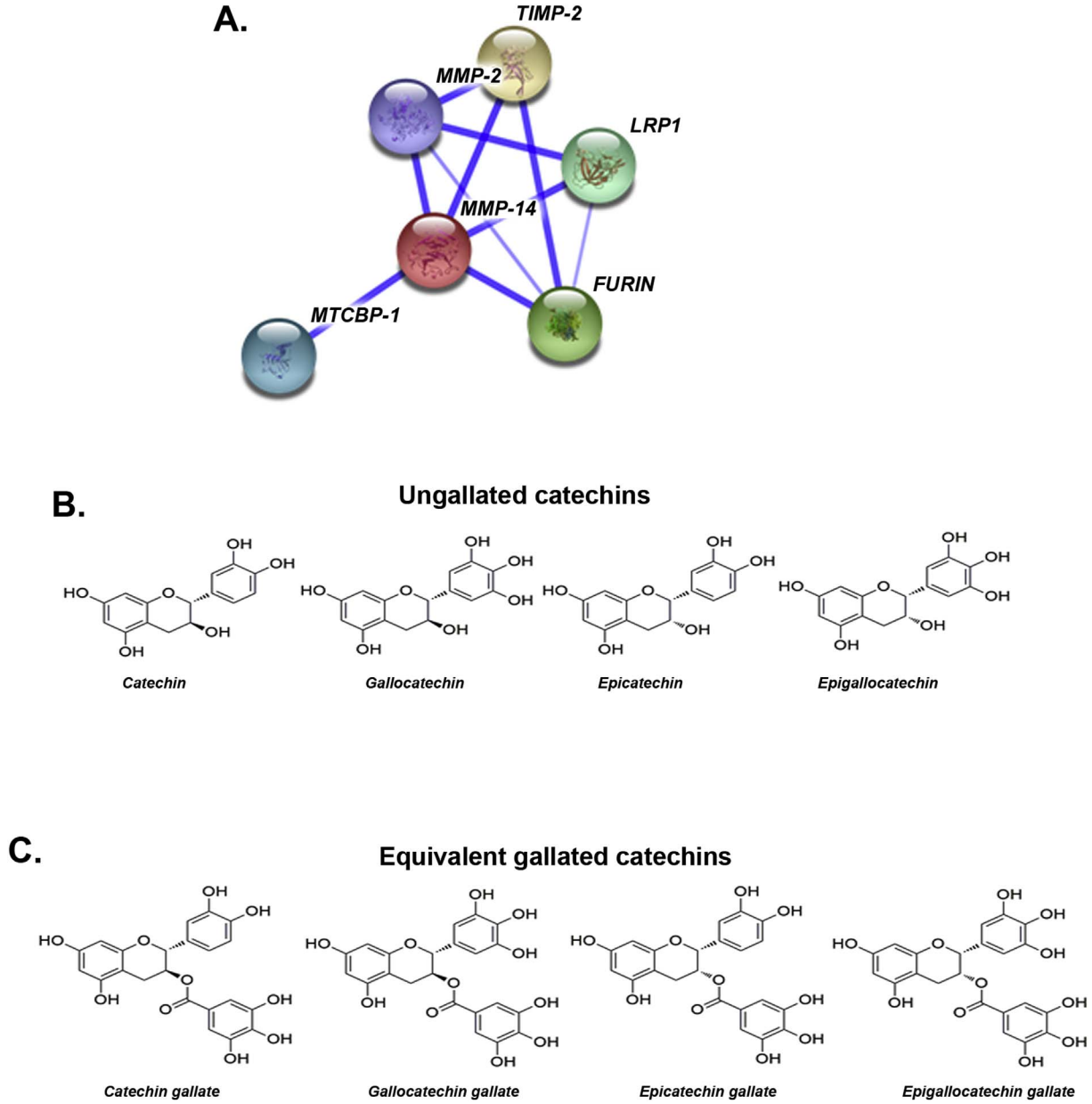

Fig. 1. Scheme of MT1-MMP predicted interactors and molecular structure of green tea-derived catechins. A) STRING V10.0 algorithm was used to identify MT1-MMP protein-protein interactors (http://string-db.org/). LRP-1, Low density lipoprotein receptor-related protein 1, MT1-MMP, membrane type-1 matrix metalloproteinase; MMP-2, matrix metalloproteinase-2, MTCBP-1, MT1-MMP cytoplasmic tail-binding protein-1; TIMP, tissue inhibitor of matrix metalloproteinase. Chemical structures of B) ungallated catechins, and C) equivalent gallated catechins which were used in cellular and acellular assays. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)