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AIN SHAMS UNIVERSITY
Faculty of Science
Zoology Department

Effect of Sodium R-Lipoate and Enzymatically-Modified Isoquercitrin on Mast Cell-Dependent Anaphylactic Reactions

A Thesis

Submitted in Partial Fulfillment for the Degree of
Master of Science in Zoology

By

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ABSTRACT

Abdel-Rahman, Gehan Waheed Abdel-Naby

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Keywords: Anaphylaxis; Compound 48/80; Enzymatically-modified isoquercitrin; Gastric ulceration; Immunoglobulin E; Mast cells; Ovalbumin; Sodium R-lipoate.

Anaphylaxis is a potentially life-threatening allergic reaction. Due to high frequency of anaphylaxis world-wide and limited benefits of using synthetic antiallergic drugs, developing of new safer and more effective therapeutic agents from natural compounds that are chemically/enzymatically-modified has become urgent challenge in improving patient's health. Therefore, the present study aimed to evaluate/compare the modulatory effects of sodium salt of R-lipoic acid (NaRLA) and enzymatically-modified isoquercitrin (EMIQ) at two different doses (50 and 100 mg/kg body weight "b.w", given orally), in a mouse models of both local/systemic immunoglobulin (Ig) E-independent and IgE-dependent anaphylactic reactions, as well as stress-induced gastric ulceration, in comparison with sulfasalazine (SSZ) as a reference drug. The data showed that the pre-treatment of mice with NaRLA or EMIQ (especially at 100 mg/kg b.w) completely succeeded, as SSZ, in reducing the hind paw edema induced by either histamine or compound 48/80 (Cpd 48/80). Furthermore, they suppressed the IgE-independent peritoneal mast cell degranulation and

anaphylactic shock caused by Cpd 48/80 (in a dose-dependent manner) and alleviated significantly ($P<0.001$) the histamine release from the mouse peritoneal mast cells, like SSZ. Also, they protected the ovalbumin (OVA)-sensitized mice from mortality in a dose-dependent manner, by reducing the elevated peritoneal histamine and interleukin-4 levels along with amelioration in the associated gastrointestinal and lung histopathological changes. This was accompanied with suppression of IgE-dependent skin mast cell degranulation as evidenced by the significant alleviation ($P<0.001$) of the active cutaneous anaphylactic reaction in the left ear of the OVA-sensitized mice. In addition, their use was associated with attenuating both gastric histopathological and biochemical alterations, as well as decreasing the percentage of degranulated mesenteric mast cells in the water-restraint stress mouse model towards the control values. In conclusion, our results provide possibility that both NaRLA and EMIQ may serve as an effective therapeutic agents for mast cells-mediated anaphylactic reactions *via* suppression of mast cell degranulation and histamine release without risks of inducing gastric ulcers.

LIST OF ABBREVIATIONS

ANOVA	One-way Analysis of Variance
APC	Antigen-presenting cell
b.w	Body weight
C5a	Complement component 5a
cAMP	Cyclic adenosine-3',5' monophosphate
CD	Cluster of differentiation
CGTase	Cyclodextrin glycosyltransferase
cNOS	Constitutive NOS
COX	Cyclooxygenase
Cpd 48/80	Compound 48/80
CRH	Corticotropin-releasing hormone
CRH-R1	CRH-receptor 1
DPX	Dibutylphthalate polystyrene xylene
ELISA	Enzyme-linked immunosorbent assay
EMIQ	Enzymatically-modified isoquercitrin
FcγR	IgG receptor
FcεRI	High-affinity IgE receptors
Glu	Glucose
GSH	Reduced glutathione
h	Hour(s)
H_2O_2	Hydrogen peroxide
HEK293	Human embryonic kidney 293 cell line
HRP	Horseradish peroxidase

Hx&E	Hematoxylin and eosin stains
i.p	Intraperitoneal
i.v	Intravenous
Ig	Immunoglobulin
IL	Interleukin
iNOS	Inducible NOS
LA	Alpha-lipoic acid
LAD2	Laboratory of allergic diseases 2
MDA	Malondialdehyde
MHC	Major histocompatibility complex
min	Minute(s)
MRGPRX2	MAS-related G-protein coupled receptor-X2
NaRLA	Sodium salt of R-LA
NFκB	Nuclear factor kappa B
NMBA	Neuromuscular blocking agent
NOS	NOx synthase
NOx	Nitric oxide
NSAID	Non-steroidal anti-inflammatory drugs
$O_2^{\bullet-}$	Superoxide anion
$^{\bullet}OH$	Hydroxyl radical
$ONOO^-$	Peroxynitrite anion
OPA	Ortho-phthalaldehyde
OVA	Ovalbumin
PAF	Platelet-activating factor
PBS	Phosphate buffered saline

PKC	Protein kinase C
PT-18	Granulocyte-macrophage colony-stimulating factor-dependent murine mast/basophil cell line
RCM	Radiocontrast media
Rha	Rhamnose
ROS	Reactive oxygen species
s.c	Subcutaneous
SCF	Stem cell factor
SCFR	Stem cell factor receptor
SEM	Standard error of mean
SSZ	Sulfasalazine
TBA	Thiobarbituric acid
TCR	T-cell receptor
Th2	T-helper 2
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha
TSLP	Thymic stromal lymphopoietin
WHO	World health organization
WRS	Water-restraint stress
$\times g$	Times gravity

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