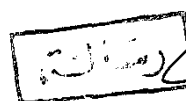




**Effect Of A Bradykinin Potentiating factor
Isolated From The Venom Of Scorpion
Buthus occitanus On Burnt Skin Of Guinea
Pig In Comparison With Other Drugs**

A Thesis



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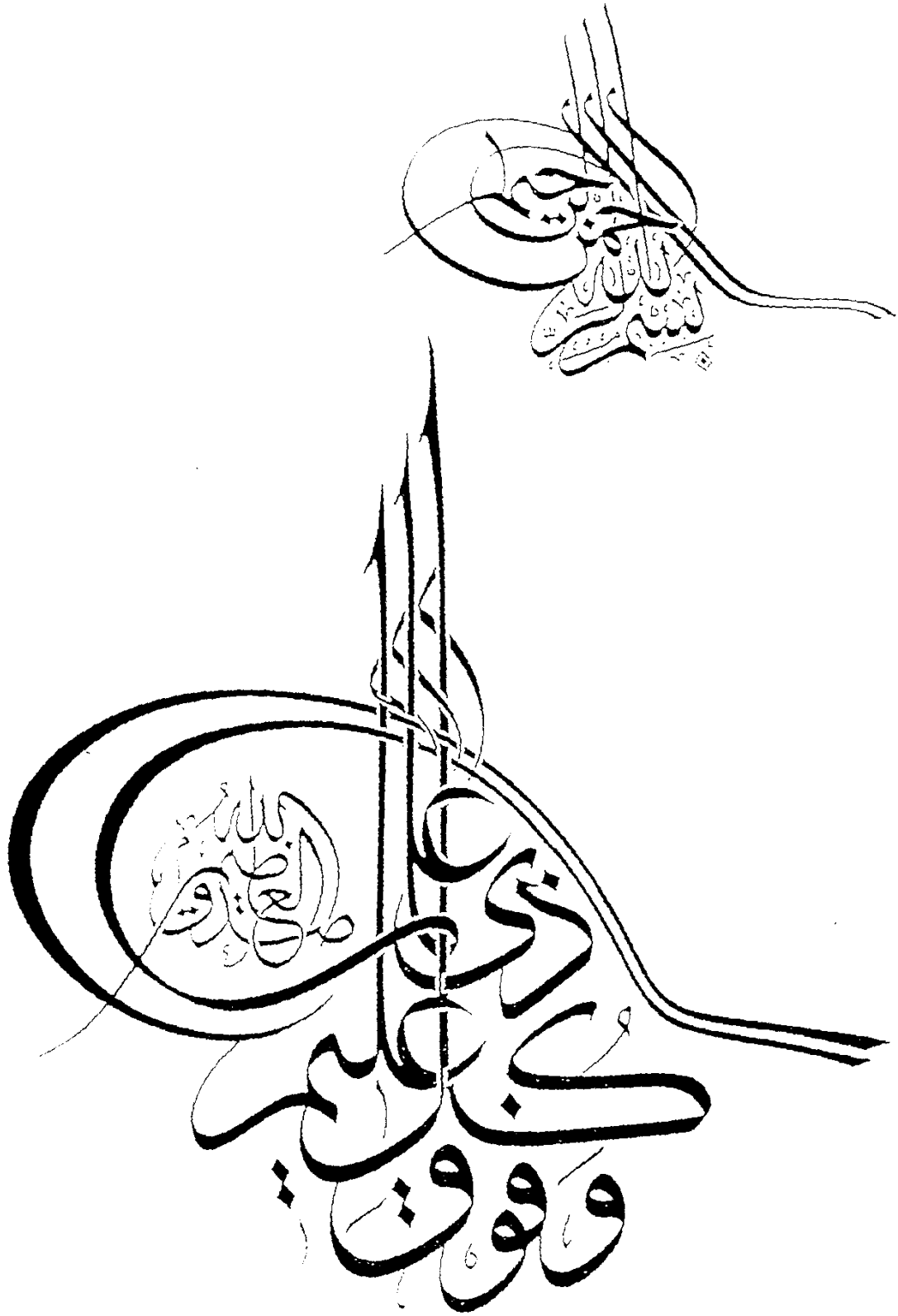
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**To
My Brothers; Abdel-Karem,
Abdel-Nasser, Khaled and
Hatim, My Wife, My Sons;
Misarah & Mazen and My
Daughter Maather**

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LIST OF ABBREVIATIONS

AA	: Arachidonic acid.
AMP	: Adenosine monophosphate.
ANG I	: Angiotensin I.
ANG II	: Angiotensin II.
ATP	: Adenosine triphosphate.
BK	: Bradykinin.
BPF(s)	: Bradykinin potentiating factor (s).
BPP(s)	: Bradykinin potentiating peptide (s).
c-AMP	: Cyclic 3,5 adenosine monophosphate.
c-GMP	: Cyclic 3,5 guanosine monophosphate.
CSF	: Colony stimulating factor.
DNA	: Deoxyribonucleic acid.
EDRF	: Endothelium relaxing factor.
EDTA	: Ethylenediaminetetra-acetic acid.
EGF	: Epidermal growth factor.
FSH	: Follicle stimulating hormone.
GH	: Growth hormone.
GMP	: Guanosine monophosphate.
ICSH	: Interstitial cell stimulating hormone.
IMP	: Inosine monophosphate.
LTs	: Leukotrienes.
LTC₄	: Leukotriene C ₄ .
LTD₄	: Leukotriene D ₄ .
PDGF	: Platelet derived growth factor.
PG(s)	: Prostaglandin(s).

PGA₂	: Prostaglandin A ₂ .
PGB₂	: Prostaglandin B ₂ .
PGD₂	: Prostaglandin D ₂ .
PGE₁, E₂ or E₃	: Prostaglandin E ₁ , E ₂ or E ₃ .
PGE₂, 9-keto-	: Prostaglandin F ₁ alpha.
PGF₂ alpha	: Prostaglandin F ₂ alpha.
PG_{G2}	: Prostaglandin G ₂
PGI₂	: Prostacyclin.
PUFA(s)	: Polyunsaturated fatty acid(s).
RIA	: Radioimmunoassay.
RNA	: Ribonucleic acid.
TSH	: Thyroid stimulating hormone.
Tx(s)	: Thromboxane(s).
TxA₂	: Thromboxane A ₂ .
TxB₂	: Thromboxane B ₂ .

INTRODUCTION AND AIM OF WORK

INTRODUCTION AND AIM OF THE WORK

Polypeptide hormones, growth factors, bioactive amines and some other substances play several roles in the regulation of mammalian cell growth and differentiation. Insulin and epidermal growth factor (EGF) are two of the most well-characterized bioactive polypeptides whose biochemical and structural properties are entirely known. There are a number of other bioactive polypeptides that are functionally and structurally related to insulin and EGF. These peptides include insulin-like growth factors (IGF-1 and IGF-11), somatomedins, multiplication stimulating activity (MSA), nerve growth factor (NGF), fibroblasts growth factor (FGF) and the EGF-like growth factors which includes various types of transforming growth factors (TGFs). Also there are some of the bioactive polypeptides that are present in serum and involved in cell growth control. This category of polypeptides includes; α_2 -macroglobulin, thrombin, transferrin and low-density lipoprotein (LDL). In addition, physiologically active prostaglandins have been found also to induce also cell division as reported by Shimizu, (1984) and Karp (1984).

The early effects of the bioactive polypeptides which appear within seconds or minutes are associated with stimulation of ion fluxes and stimulation of enzymes involved in glycolysis, lipid metabolism and glycogen

synthesis. The delayed effects which may appear several hours after ligand binding, include the stimulation of protein, RNA and DNA synthesis; and cell division (Shimizu, 1984). The signals which correlate with the early or delayed cellular effects of the polypeptides involve glucose transporting system, Ca^{2+} ion and diacylglycerol as second messengers, chemical mediators, phosphorylation reaction, polyamines, adenosine diphosphate-ribosylation reaction and cytoskeletal change (Shimizu, 1984). Boucek and Noble (1973) found that histamine, norepinephrine and serotonin enhance fibroblastic growth. They suggested different mechanisms for interpreting the action of these compounds. Their effect may be directed to the cellular levels of adenosine triphosphate and or/cyclic nucleotide monophosphates. Moreover, serotonin has been reported to be associated with ATP formation in a variety of cells and it is reported to stimulate oxidative phosphorylation of rat mitochondria (Warashima and Hoppe-Seylers, 1967). Furthermore, Abu-Sinna in 1983 announced that indole-3-acetic acid and the chemically related compounds, serotonin, tryptophan, indole-pyruvic, indole-butyric and tryptamine can increase the number of human fibroblasts and 3T3 cells cultivated *in vitro* probably through c AMP- c GMP system.

In skin burns or other skin injuries there is a rapid release of bradykinin, serotonin and histamine which play

a pathogenic role in tissue injury and inflammation (Rocha e Silva and Rosenthal 1961; Starr & West, 1967 and Maccreau et al., 1983). The granular components of mast cells include histamine, serotonin, bradykinin, prostaglandins and leukotrienes (Blood and Haegermark, 1965; Jansson, 1969 and Uvnas, 1978). These bioactive substances act by increasing intracellular concentration of Ca^{2+} (Berridge, 1984 and 1985) which binds to calmodulin to form the active Ca^{2+} -calmodulin complex. This complex inturn, activates the membrane-bound phospholipase A_2 (Wong and Cheung, 1979; Craven and DeRubertis, 1983 and Moskowitz et al., 1983) that could be markedly activated by bradykinin and histamine (Ziboh and Lord, 1979).

Generally, kinins are believed to act as mitogens stimulating DNA synthesis and cell division (Rixon et al., 1973 and Marceau et al., 1986). Intradermal occlusions of the sweat gland duct unit together with the migration of neutrophils into pustules and microabscesses may results in an increased formation of the peptide. (Neuman, 1974 and Dawber, 1981). The higher kinin levels could in part account for the increased mitotic activity seen in the psoriatic epidermis (Poblete, 1991). However, little is known about the exact role that kinins play on growth promotion.

Alternatively; some reports suggest that Aloe vera may have an effective antibacterial action (Robson et al.,

1982). An added benefit of its topical antimicrobial action is that it also acts as inhibitor of thromboxane production (Robson et al., 1984) which could provide unquestionable advantages in the management of burn wounds. Since blocking the formation of vasoactive prostanoids prevents the vasoconstriction, thrombosis and progressive ischemic necrosis known to occur in thermal and electrical burns as a result of unbalanced thromboxane production. Basically, the use of Aloe vera could result in preventing the progressive nature of thermal injury as well as controlling bacterial growth in the burn wound.

Bradykinin potentiation could be pharmacologically achieved by some thio-compounds such as dimercaprol, (Ferreira & Rocha e Silva, 1962 and Corrado, 1963). Ferreira, in 1965 announced that a bradykinin potentiating factor (BPF); has been isolated from the venom of the Brazilian snake, *Bothrop jararaca* and added that venom fraction is the most effective bradykinin potentiator so far described. Nassar et al. (1989) isolated the same fraction from the venom of the Egyptian scorpion; *Buthus occitanus*. The fraction was found to exhibit a potentiating activity on cellular growth of ovarian follicles and endometrium of mice (Nassar et al., 1990) as well as spermatogenesis (Nassar et al., 1992).

Since, one of the clinical goals for growth factors is to accelerate healing in normal wound, to initiate