

**EFFECT OF PREBIOTICS SUPPLEMENTAED MILK
FORMULA ON THE SERUM LEVEL OF INTERLUEKIN-1
AND INTERLUEKIN-6 IN INFANTS**

Thesis

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List of Abbreviations (Cont...)

SCFA	Short-chain fatty acids
SF	Standard formula
Th1	T helper 1
Th2	T helper 2
TNF	Tumor Necrotic Factor
WHO	World Health Organization

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List of Abbreviations

BF	Breast feeding
BMI	Body Mass Index
CRP	C reactive protein
D-MER	Dysphoric Milk Ejection Reflex
FFDCA	Federal Food, Drug, and Cosmetic Act
FOS	Fructo-oligosaccharides
GALT	Gut-associated lymphoid tissue
GI	Gastrointestinal
GIT	Gastrointestinal tract
GOS	Galacto-oligosaccharides
HMOS	Human milk oligosaccharides
IBD	Inflammatory bowel disease
IBS-C	Irritable bowel syndrome with constipation
IBS-D	Irritable bowel syndrome with diarrhea
IgA	Immunoglobulin A
IL-1	Interleukin-1
IL -6	Interlukin 6
NEC	Necrotizing enterocolitis
OF	Oligofructose
Pre	Prebiotics
PDX	Polydextrose
PP	Peyer's patches
PG E2	Prostaglandin E2

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INTRODUCTION

Prebiotics are selectively fermented non-digestible food ingredients that were identified and named by Marcel Roberfroid. They allow specific changes both in the composition and/or activity of the gastrointestinal microflora that confers benefits upon host well-being and health. Roberfroid stated that only the particular fructo-oligosaccharides fully meet this definition are the oligofructose and inulin. Other authorities also classify galactooligosaccharides (GOS) as prebiotics. Also, Mannan oligosaccharides (MOS) have been termed as immuno-saccharides (*Roberfroid, 1995*).

Prebiotics are natural energy source for the growth of healthy bacteria in the gut. This growth supports the infant's natural defences by increasing the levels of healthy bacteria and decreasing the levels of potentially harmful bacteria found in the intestine, positively influencing the entire microbiota (*Haarman, 2005*). Prebiotics are specifically formulated in milk formulas to mimic the effect of oligosaccharides naturally present in breast milk, the effect being similar to seen in infants who are breast fed. Prebiotics are therefore important for any infant who is not breast fed, as they have a natural, positive effect on the entire gut microbiota, helping to support the infant's immune system and have an effect on gastrointestinal motility (*Haarman, 2005*).

The gastrointestinal tract (GIT) microbiota plays an important role in host health due to its involvement in nutritional,

immunologic and physiological functions. Microbial imbalances have been associated with enhanced risk of specific diseases (*Collado et al., 2009*).

Probiotics and prebiotics alone or together (synbiotics) can influence the intestinal microbiota and modulate the immune response. They may therefore be tools that can prevent or alleviate certain pathologies involving the gut immune system such as allergies for which no treatment is yet available (*Gourbeyre et al., 2011*). Prebiotics can also exert an influence on the gut immune system via the stimulation of the bacterial metabolism (*Gourbeyre et al., 2011*).

Interleukin-1 alpha (IL-1 α) is a protein of the interleukin-1 family that in humans is encoded by the IL1A gene. In general, Interleukin 1 is responsible for the production of inflammation, as well as the promotion of fever and sepsis. IL-1 α inhibitors are being developed to interrupt those processes and treat diseases (*Nicklin et al., 1994*).

IL-1 α is produced mainly by activated macrophages, as well as neutrophils, epithelial cells, and endothelial cells. It possesses metabolic, physiological, haematopoietic activities, and plays one of the central roles in the regulation of the immune responses. It binds to the interleukin-1 receptor, IL-1 α is a cytokine of the interleukin-1 family (*Bankers-Fulbright et al., 1996*).

IL-6 is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation (**Ferguson-Smith et al., 1988**).

IL-6 is one of the most important mediators of fever and of the acute phase response. It is capable of crossing the blood brain barrier and initiating synthesis of PGE₂ in the hypothalamus, thereby changing the body's temperature setpoint (**Banks et al., 1994**).

IL-6 is responsible for stimulating acute phase protein synthesis, as well as the production of neutrophils in the bone marrow. It supports the growth of B cells and is antagonistic to regulatory T cells (**Benedict et al., 2009**).

AIM OF THE WORK

This study was done to evaluate efficacy, tolerability & safety of prebiotics milk formula as well as to study its impact on inflammatory markers as serum level of interleukin 1 (IL- 1) & interleukin 6 (IL- 6).

BREASTFEEDING

Introduction:

Breastfeeding is the feeding of an infant or young child with breast milk directly from female human breasts (i.e., via lactation) rather than from a baby bottle or other container. Babies have a sucking reflex that enables them to suck and swallow milk. It is recommended that mothers breastfeed for six months or more, without the addition of infant formula or solid food. After the addition of solid food, mothers are advised to continue breastfeeding for at least a year, and can continue for two years or more. Human breast milk is the healthiest form of milk for babies (*Picciano, 2001*).

One of the most important decisions a mother has to do before her infant is born is to decide whether that infant will be breast fed or formula fed human milk is uniquely adapted to infant's need, thus all mothers should be encouraged to breast feed her baby (*Heird et al., 2004*).

Experts agree that breastfeeding is beneficial and have concerns about artificial formulas but there are conflicting views about how long exclusive breastfeeding remains beneficial (*Baker , 2003*).

The World Health Organization (WHO) and the American Academy of Pediatrics (AAP) emphasize the value of breastfeeding for mothers as well as for children. Both recommend exclusive

breastfeeding for the first six months of life. The AAP recommends that this should be followed by supplemented breastfeeding for at least one year, while WHO recommends that supplemented breastfeeding continue up to two years or more (*Gartner et al., 2005*).

Human breast milk

Production:

Composition:

During the first few days after delivery, the breasts produce colostrum. This is a thin yellowish fluid that is the same fluid that leaks from the breasts during pregnancy. It is rich in protein and antibodies that provide passive immunity to the baby (the baby's immune system is not fully developed at birth). Colostrum also helps the newborn's digestive system to grow and function properly.

After 3 to 4 days, breasts will begin producing milk that is thin, watery, and sweet. This quenches the baby's thirst and provides the proteins, sugar, and minerals that the baby needs. Over time, the milk changes and becomes thick and creamy. This satisfies the baby's hunger.

Foremilk, the milk released at the beginning of a feed, is watery, low in fat, and high in carbohydrates relative to the creamier hind milk, which is released as the feed progresses. The breast can never be truly "emptied," since milk production is a continuous biological process.

The level of Immunoglobulin A (IgA) in breast milk remains high from day 10 until at least 7.5 months post-partum (*Rechtman et al., 2002*).

Table (1): Comparison of Human, cow's milk and standard formula.

Nutrients	Human Colostrum	Human mature milk	Cow's milk	Standard formula
Kcal/100ml	67	67	67	67
CHO (Lactose- gm/dl)	5.7	7.1	4.7	7.0 - 8.5
Protein (gm/dl)	2.9	1.06	3.1	1.5 - 2.2
Whey : caesin	80 : 20	0	18 : 82	60 : 40
Fat (gm/dl)	2.95	4.54	3.8	3.5 - 4.5
Sodium (g/l)	0.50	0.17	0.77	0.25
Potassium (g/l)	0.74	0.51	1.43	0.80
Chloride (g/l)	0.59	0.37	1.08	.057
Calcium (g/l)	0.48	0.34	1.37	46 – 73
Phosphorus (g/l)	0.16	0.14	0.91	32 – 56
Calcium/ Phosphorus	3.1	2.4	1.5	1.3 - 1.5
Magnesium (g/l)	0.04	0.03	0.13	5.6
Copper (mg/l)	1.34	0.51	0.10	0.40
Zinc (mg/l)	5.59	1.18	3.90	5.0
Iodine (mg/l)	0	0.06	0.08	0.01
Iron (mg/l)	1.0	0.50	0.45	0.15
Vitamin A (mg/l)	1.61	0.61	0.27	1.5
Vitamin D (iu)	0	4 - 100	5 -40	41 – 50
Tocopherol (mg/l)	14.8	2.4	0.6	8.liu
Thiamine (mg/l)	0.02	0.14	0.43	0.47
Riboflavin (mg/l)	0.30	0.37	1.56	1.0
VitaminB6 (mg/l)	0.0	0.18	0.51	0.50
Nicotinic Acid (mg/l)	0.75	1.83	0.74	6.7
Vitamin B12 (ug/l)	0.06	0.34	2.48	2.0
Pantothenic acid (mg/l)	1.83	2.46	3.4	3.0
Folic acid (ug/l)	5.0	14.0	90.0	10 – 13
Vitamin C (mg/l)	72	52	11	6.7
Osmolality	290 - 300	0	0	300 – 380

(Constituents of human milk United Nations University Centre).

Benefits of breast feeding

Feeding is species specific, and all substitute feeding preparations differ markedly from it making human milk uniquely superior for infant feeding (*American academy of pediatrics, 2005*).

Also the benefits attributable to breast feeding may persist past infancy (*Fulhan et al., 2003*).

Exclusive breast feeding is the reference or nonnative model against which all alternative feeding methods must be measured with regards to growth, development, and all short term and long term outcomes (*Bier et al., 2002*).

A- Benefits for the infant

Greater immune health:

Oral antigens are normally processed in a manner that results in a regulated immune response that maintains oral tolerance (*Akdis et al., 2004 and Wang et al., 2008*).

In the neonatal period, the infant immune system is limited in the ability to mount an efficient immune response. This impairment is present in a number of functions in the immune system associated with mounting effective immune responses to pathogens or allergens. The neonatal immune system also has a preference for T helper 2 (Th2), as opposed to T helper 1 (Th1) cytokines (*Wang et al., 2008 and Holt et al., 2000*).

Maternal milk and/or formula provide nutrition for newborn infants. Maternal milk is not only a source of nutrition
