ALIMENT FONCTIONNEL, EFFICACE, SÛR, ET FIABLE,
VERIFIÉ SCIENTIFIQUEMENT, DERIVÉ DU SON DE RIZ

IMMUNOMODULATEUR™
FIABLE ET EPROUVÉ

ImunoBran®

GUIDE

COMPOSANT D'ARABINOXYLANE DE SON DE RIZ

SOMMAIRE

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1. INTRODUCTION

L'ImunoBran est un aliment efficace produit à l'aide d'un composant de fibres du son de riz soluble dans l'eau (hémicelluloses B). Des recherches effectuées sous la conduite du Professeur Mamdooh Ghoneum PhD. de l'Université de Californie de Los Angeles, Etats-Unis (UCLA/Drew University of Medicine and Science) et concentrées sur les composants de fibres du son de riz ont abouti à la découverte et mise au point de méthodes de traitement et de production d'un aliment qui module de manière optimale le fonctionnement de l'immunité innée du corps. Il s'est avéré plus tard que l'ImunoBran possède un effet non seulement immunostimulateur mais également immunomodulateur™. Le résultat de cet important effort de maximiser la stabilité et le goût du produit est un arabinoxylane de son de riz – l'ImunoBran. A l'heure actuelle, l'ImunoBran est appliqué non seulement au Japon, mais aussi dans 50 autres pays du monde entier et jouit d'une excellente réputation.

La fibre et les autres composantes indigestes des aliments sont considérées comme des substances ayant une forte influence sur la santé de l'homme, ayant un effet bénéfique sur le maintien de l'homéostasie et remplissant dans le corps des tâches thérapeutiques différentes de celles qu'assurent les nutriments de base. Leur activité principale consiste à améliorer le métabolisme des graisses, le métabolisme des sucres et à améliorer le milieu intestinal, ainsi que d'inhiber la toxicité des substances dangereuses contenues dans l'alimentation.

La fibre que l'on trouve dans nos aliments provient avant tout des plantes, des algues et des micro-organismes, et une autre partie est créée par les polymères des sucres - les polysaccharides. De nombreuses études font état de l'activité immunostimulante des polysaccharides des aliments et des micro-organismes de fermentation, ce qui a conduit à l'introduction d'une notion à part pour ces substances – les modificateurs de la réponse biologique (en anglais BRM).En font partie les polysaccharides tels que le zymosane (β-1-3 glucane), composant constructeur des parois cellulaires des levures de bière, la chitine, ou encore le composant constructeur des parois cellulaires des levures de boulanger (α-1-6-mannan) et les éléments de construction des parois cellulaires de champignons tels que le Shiitake (lentin comestible), le Suehirotaké (schizophylle commun) et le Kawarataké (Polypore versicolore) (contenant duβ-1-3 glucane), etc. Certaines de ces substances sont utilisées dans le traitement du cancer comme immunostimulateur administrés le plus souvent sous forme de piqûres intraveineuses étant donné leur masse moléculaire relativement élevée (0,5-1 millions de daltons) qui leur est caractéristique et qui, si administrés par voie orale, en restreint les effets.

Au vu des informations scientifiques acquises au sujet des polysaccharides et de leurs potentiels immunostimulants, l'ImunoBran MGN-3 a été développé de façon ciblée comme un complément alimentaire immunostimulateur capable d'agir lorsqu'il est administré par voie orale.

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2. IMUNOBRAN – ARRIÈRE-PLAN DU DÉVELOPPEMENT DU PRODUIT

L'état du corps humain est maintenu à un niveau constant grâce à la régulation de la température du corps et de la tension artérielle de façon à ce qu'il maîtrise les changements de milieu à l'intérieur comme à l'extérieur de l'organisme. Ce mécanisme s'appelle l'homéostasie. Lors de l'homéostasie, le système immunitaire inné qui élimine les substances étrangères (impropres à l'organisme) telles que agents pathogènes, virus et cellules cancéreuses joue un rôle important. L'on sait que le fonctionnement de l'immunité se dégrade au fur et à mesure de l'âge, et que le mauvais style de vie et ses phénomènes accompagnateurs comme le tabagisme, le manque d'exercice physique, le déséquilibre alimentaire, ou encore les influences négatives de l'environnement et la pollution réduisent, voire stimulent de manière inadéquate l'immunité. Le dysfonctionnement de l'immunité contribue à la propagation ou à l'empirement des infections et des tumeurs malignes tandis que l'irritation trop importante du système immunitaire peut causer des problèmes tels que le rhume des foins, l'eczéma atopique ou l'infection chronique.
La société Daiwa Pharmaceutical Co., Ltd., pressentant l'influence potentielle de la fibre sur la réponse immunitaire de l'organisme, s'est concentrée justement sur cet aspect et a développé un aliment multifonctionnel ayant beaucoup en commun avec les aliments que les Japonais consommaient jadis, et a appelé son produit ImunoBran (composant d'arabinoxylane de son de riz).

3. IMUNOBRAN – PROCESSUS DE FABRICATION

Le composant principal de la fabrication de l'ImunoBran est une fibre soluble dans l'eau (l'hémicellulose B) représentant à peu près 5 % du volume de son de riz. L'hémicellulose B du son de riz est une fibre composée d'arabinose et de xylose caractéristique par sa structure compliquée et par sa masse moléculaire relativement faible. L'hémicellulose B du son de riz se digère mal sous sa forme naturelle et ne présente aucun effet immunostimulateur ni autre.
Cependant il s'est avéré que, lorsque cette substance est hydrolysée partiellement par un complexe enzymatique hydrolytique d'hydrate de carbone obtenu à partir de cultures de mycélium du champignon shiitake, elle se transforme en une substance aux effets immunostimulateur. Contrairement à d'autres matériaux contenant de l'arabinoxylane, l'ImunoBran est un produit alimentaire unique en son genre de par son processus de fabrication innovant développé par la compagnie Daiwa Pharmaceutical Co., Ltd.

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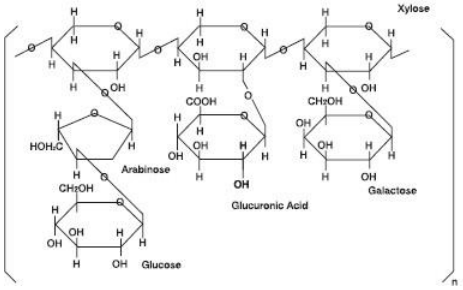
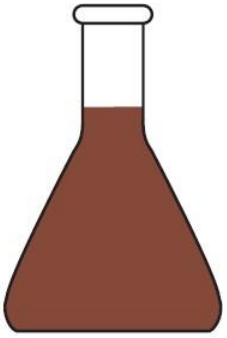
Son de riz (Fig.)

Extraction en eau chaude



Culture de mycélium de shiitake

Mycélium ôté du champignon shiitake



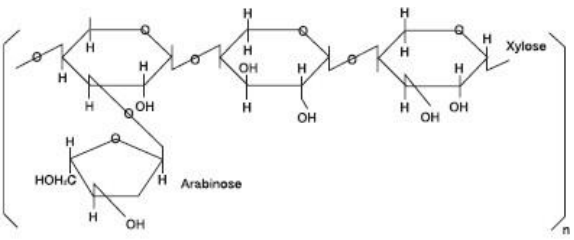
Texte du schéma de la formule:
xylose, arabinose, acide gluconique, galactose, glucose

Fibre soluble dans l'eau (hémicellulose B)

Complexe enzymatique hydrolytique d'hydrate de carbone

Modèles structuraux d'arabinoxylane et semblables dérivés

Activation



Modèle structural de l'ImunoBran (arabinoxylane de son de riz).

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4. INFORMATIONS SUR LE PRODUIT

ImunoBran 250 (50comprimés)
Chaque comprimé contient 250 mg de MGN-3 composé d'arabinoxylane
Poids Net: 22,5 g sous la forme de 50 comprimés x 450mg
Prix de 54€

ImunoBran 1000 (30 sachets)
Chaque sachet contient 1000 mg de MGN-3 composé d'arabinoxylane
Poids Net: 60g sous la forme de 30 sachets de 2g
Prix de 130€

ImunoBran 1000 (105 sachets)
Chaque sachet contient 1000 mg de MGN-3 composé d'arabinoxylane
Poids Net: 210g sous la forme de 105 sachets de 2g
Prix de 430 €

4.1. Spécifications qualitatives

Valeur testée	Spécification
Description	Poudre marron clair
Eau	≤ 8 %
Protéine	8 – 15 %
Cendre	5 – 10 %
Hydrate de carbone	65 – 80 %
Arsenic (sous forme AS_2O_3)	≤ 5,0 ppm*
Métal lourd (Pb)	≤ 20 ppm
Nb. total de cellules vivantes	≤ 3×10^3 CFU/g*
Bactéries coliformes	négatif

*ppm – partie par million, *CFU – unité formant colonie dans 1 gramme

4.2. Propriétés

Facilement soluble dans l'eau et thermostable.

4.3. Conservation

Le produit est fortement hygroscopique. Préservez-le donc fermé et à l'abri des hautes températures et de l'humidité.

4.4. Le goût du produit

L´ImunoBran MGN-3 fait partie des compléments alimentaires les plus sûrs sur le marché avec une histoire d'enregistrements cliniques de presque 15 ans. Il n'est pas toxique (LD50 >36,0 g/kg) et est bien toléré, n'a pas de goût ni d'arôme désagréables, et ne provoque pas de dégoût. Malgré le fait que, dans le processus de fabrication, des enzymes de champignon participent à la fission de la fibre de son de riz, le produit final est toléré sans problème par les personnes qui autrement ne supportent pas les champignons.

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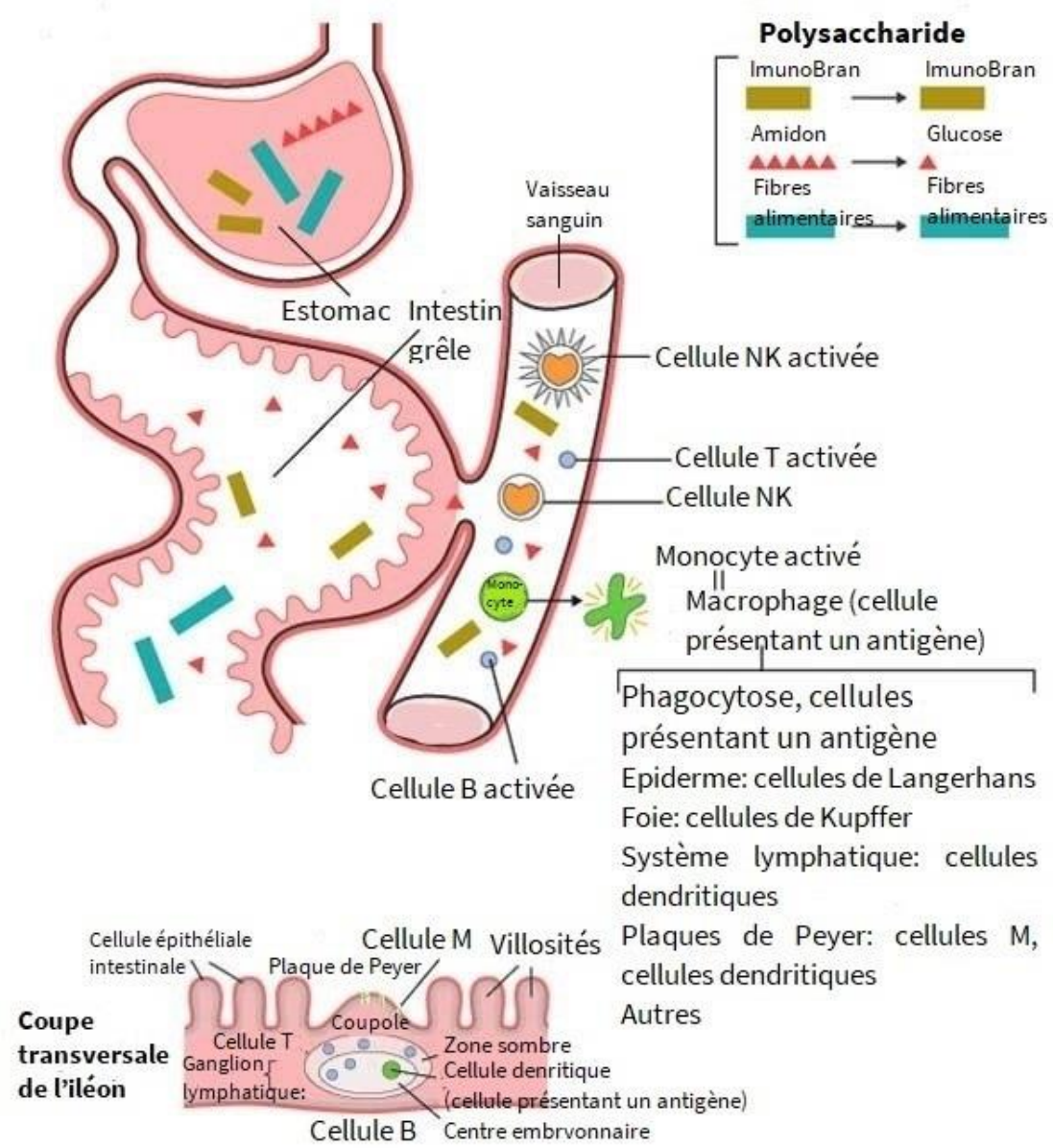
5. IMUNOBRAN – MÉCANISME DE FONCTIONNEMENT

L'amidon, la fibre, tout comme l'ImunoBran font partie des polysaccharides.
L'amidon est digéré par la salive, les sucs intestinaux et pancréatiques et est finalement absorbé sous forme de glucose dans l'intestin grêle. L'organisme humain ne digère pas la fibre et l'expulse non modifié. D'après les informations dont on dispose, l'ImunoBran peut être partiellement absorbé directement dans l'appareil digestif puis dans le système sanguin où il active directement ou indirectement les cellules NK par les plaques de Peyer dans l'iléon, les cellules T, les cellules B et les macrophages, et joue ainsi un rôle important dans l'immunomodulation (dans les processus immunostimulateur, anti-inflammatoires, antiallergiques et antioxydants). Il est établi qu'il améliore dans l'ensemble les facultés naturelles thérapeutiques de l'organisme, réduit les réactions indésirables de la chimiothérapie et assure une meilleure qualité de vie.



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6. SÉCURITÉ

6.1. Études de toxicologie et de sécurité

6.1.1. Test de mutagénéité (Ames test)

L'ImunoBran a été soumis au test bactérien de mutation réversive jusqu'à une concentration de 10 000 µg/lamelle dont il est ressorti avec un résultat négatif, que ce soit avec ou sans stimulation métabolique.

Réalisé par Consumer Product Testing Company, NJ, USA

6.1.2. Test de dose unique sur rats

L'on a administré à des rats mâles et femelles Wistar une dose unique de l'ImunoBran aux concentrations de 5, 10, 18, et 36 g/kg. Aucun des rats n'est mort et c'est donc la concentration de 36 g/kg ou de valeur supérieure qui est considérée comme LD_{50}.

Réalisé par AMA Laboratories, Inc. NY, USA

6.1.3. Administration répétée de l'ImunoBran chez les chiens

Dans le cadre de l'étude de la sécurité de l'ImunoBran effectuée sur les chiens, il a été administré aux chiens et chiennes de la race beagle des doses de 0, 20, et 200 mg/kg de l'ImunoBran mélangées à la potée une fois par jour pendant 4 semaines (28 doses). Aucun résultat anormal quant à la condition, le poids, la prise de nourriture, l'hématologie ou la biochimie sanguine n'a été relevé ni après 4 semaines d'absorption du produit en doses de 20 et 200 mg/kg par jour. Dans le cadre de cette étude le NOAEL (dose sans effet toxique) du produit est établie à 200 mg/kg par jour ou plus.

Réalisé par l'Institut Kyodoken. Kyoto, Japon

6.2. Contre-indication

L'unique (et évidente) contre-indication du produit ImunoBran MGN-3 est l'utilisation simultanée d'immunosuppresseurs. Il est évident que nous ne pouvons pas vouloir renforcer l'immunité si, d'un autre côté, notre médecin tente de la réduire par des médicaments. Outre cette exception, le produit n'est pas contre-indiqué quant à la prise d'autres médicaments et autres compléments alimentaires. Cependant nous recommandons aux patients de toujours consulter leur médecin avant d'utiliser le produit.

6.3. Brevets

JAPON	Brevet n°. 3519187
ÉTATS-UNIS	Brevet n°. 5560914
EUROPE (LUXEMBOURG, FRANCE, ROYAUME-UNI, ESPAGNE, ITALIE, BELGIQUE, ALLEMAGNE, PORTUGAL)	Brevet n°. 753582
CORÉE	Brevet n°. 0344755

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7. DOSAGE RECOMMANDÉ PAR JOUR

Vu les résultats des études effectuées sur les animaux et les humains, le dosage recommandé est de 1 à 3g par jour ou 4 comprimés 1 à 3g par jour environ 20 minutes avant ou une demi-heure après un repas.
La dose recommandée a été déterminée par l'étude clinique suivante.

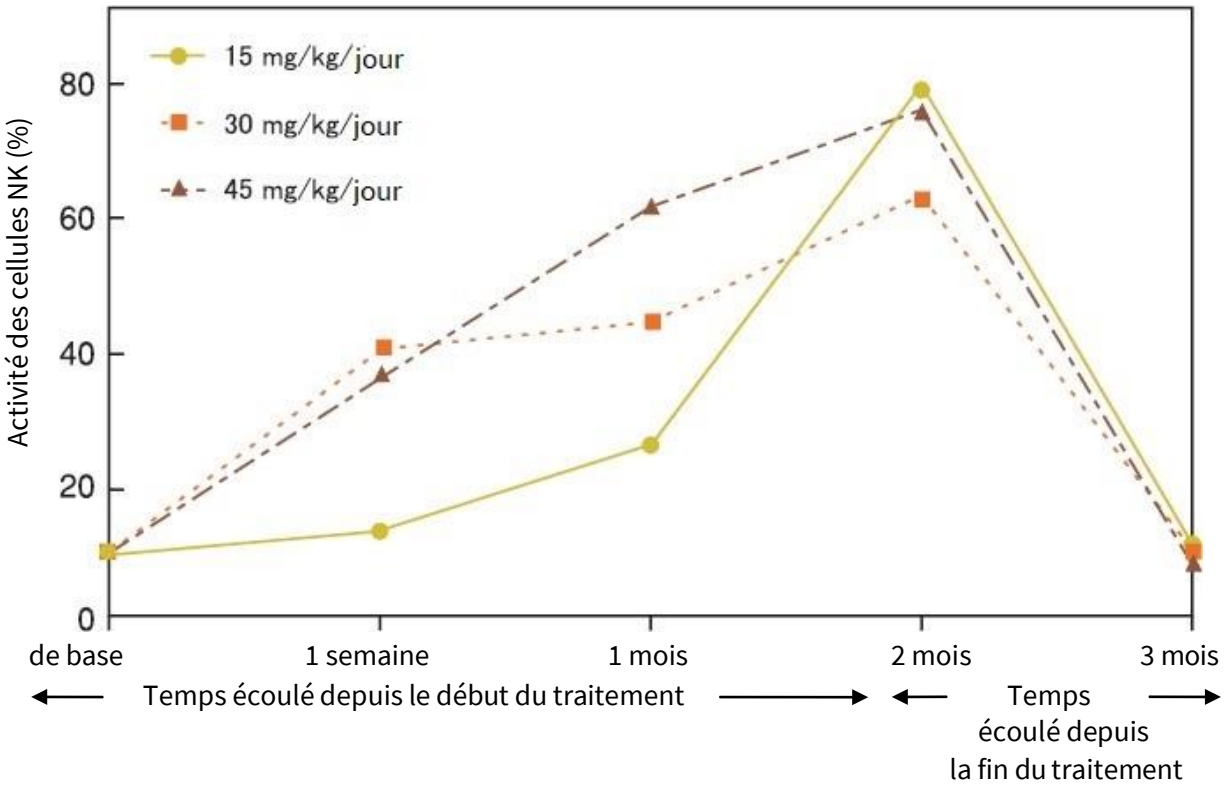
8. UTILISATION DU PRODUIT EN TANT QU'ALIMENT FONCTIONNEL

8.1. Activité immunomodulatrice

8.1.1. Activation des cellules NK humaines en réaction à l'ImunoBran

Nous avons prescrit à vingt-quatre personnes portées volontaires divisées en trois groupes de 8 une prise pérorale de l'ImunoBran en doses de 15 mg/kg de masse corporelle (équivalant environ à 1 g du produit), 30 mg/kg de masse corporelle (équivalant à 2 g), voire 45 mg/kg de masse corporelle (équivalant environ à 3 g) par jour sur une durée de deux mois, puis nous avons mesuré l'effet du produit sur l'activité des cellules NK.
Dans le groupe des 15 mg/kg, l'activité n'a presque pas changé au bout d'une semaine, par contre, elle a presque doublé par rapport à l'activité de base. Dans le groupe des 30 mg/kg, l'activité a triplé en une semaine par rapport à l'activité de base et a progressivement augmenté jusqu'à cinq fois, au bout de 2 mois. Dans le groupe des 45 mg/kg, une évolution semblable à celle du groupe des 30 mg/kg a été notée dans une mesure et une intensité toutefois plus importantes. Après l'arrêt du traitement le niveau d'activité des cellules NK est revenu petit-à-petit à celui des valeurs de base.

Texte du graphe de la page 6 :
Temps des changements de l'activité des cellules NK après absorption de l'ImunoBran.



Ghoneum M., Drew Univ., „Amélioration de l'activité des cellules NK humaines suite à la prise d'Arabinoxylane modifié de son de riz (MGN-3) ", INT.J. IMMUNOTHERAPY XIV(2) p. 89-99, 1998

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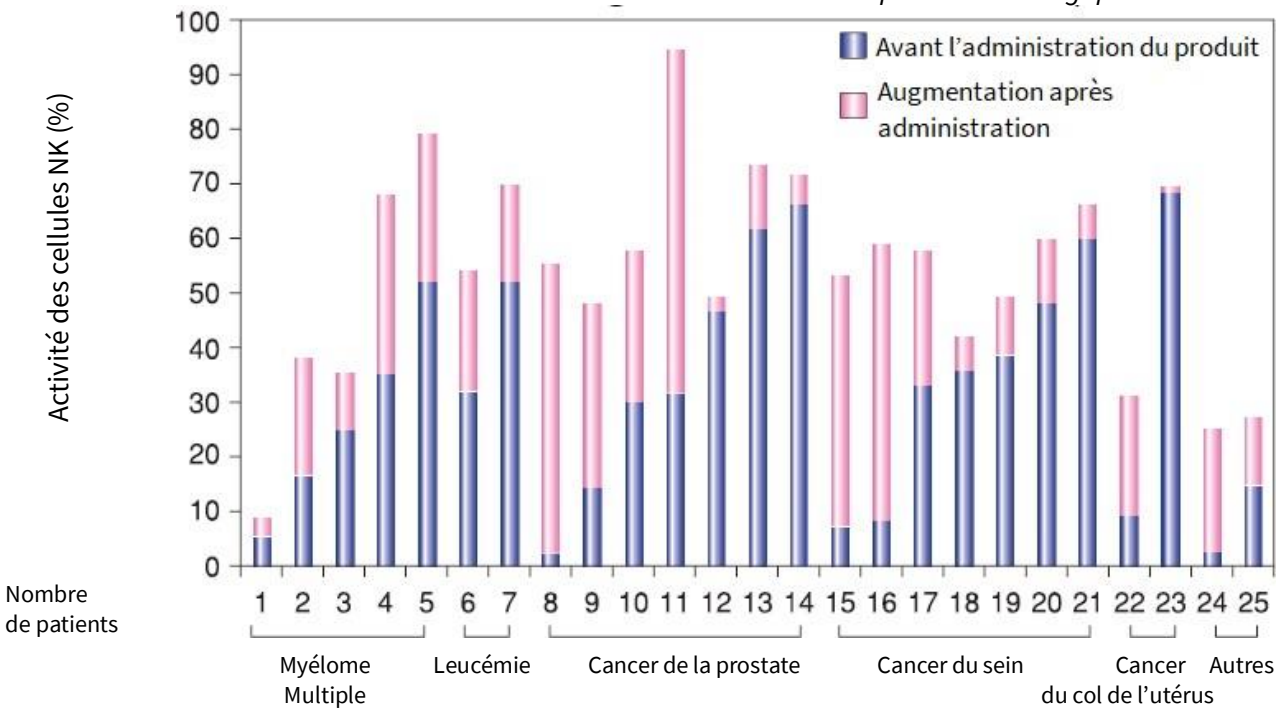
8.1.2. Activation des cellules NK chez les patients oncologiques après absorption de l'ImunoBran

Nous avons administré de l'ImunoBran à 25 patients oncologiques en stades progressifs de la maladie et soignés par chimiothérapie, intervention chirurgicale ou traitement hormonal sur une période de 6 mois et avons ensuite comparé l'activité des cellules NK à leur activité de la période précédant l'application du produit. Même si les valeurs de base étaient très différentes chez la plupart d'entre eux, il a été constaté chez tous une augmentation des cellules NK après l'administration de l'ImunoBran.

Effet d'activation de l'ImunoBran sur l'activité des cellules NK chez les patients oncologiques.

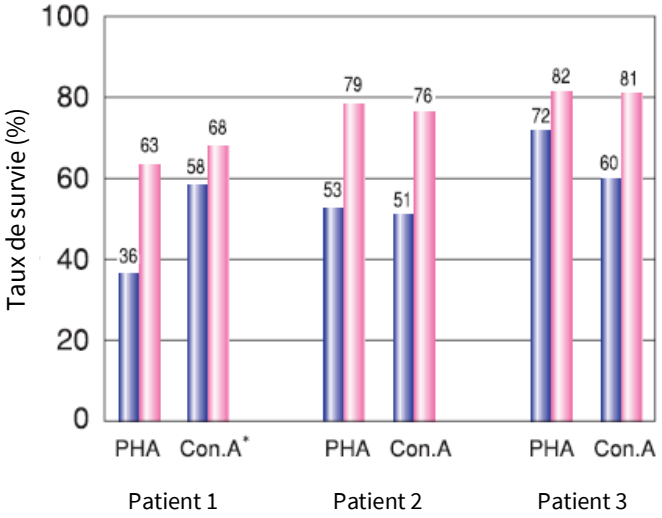


Ghoneum M. et G. Namatalla,- 87e réunion annuelle de l'Association américaine pour la recherche du cancer 1996

8.1.3 Stimulation de la transformation des lymphocytes

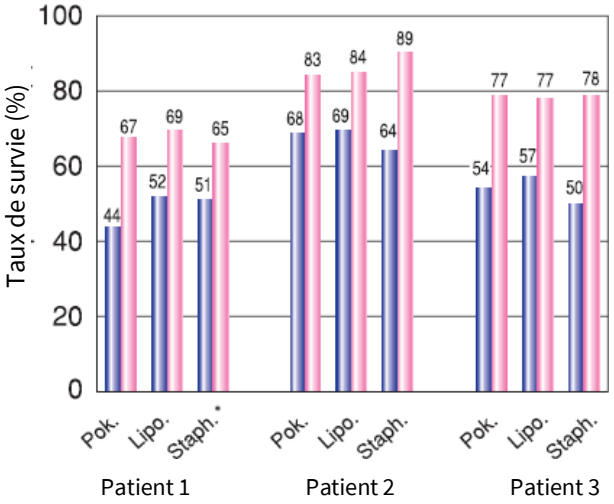
On a comparé la survie des lymphocytes T et B avant et après administration de l'ImunoBran, et il a été noté chez 3 patients que la survie des deux types de cellules s'était accrue après l'administration dudit produit.

Effet de l'ImunoBran sur la survie des cellules T.



* PHA et Con. A sont des mitogènes

Effet de l'ImunoBran sur la survie des cellules B



* Pok., Lipo. et Staph. sont des mitogènes

Avant administration de l'ImunoBran Après administration de l'ImunoBran

Ghoneum M., 11e conférence annuelle sur le SIDA, Vancouver, 1996

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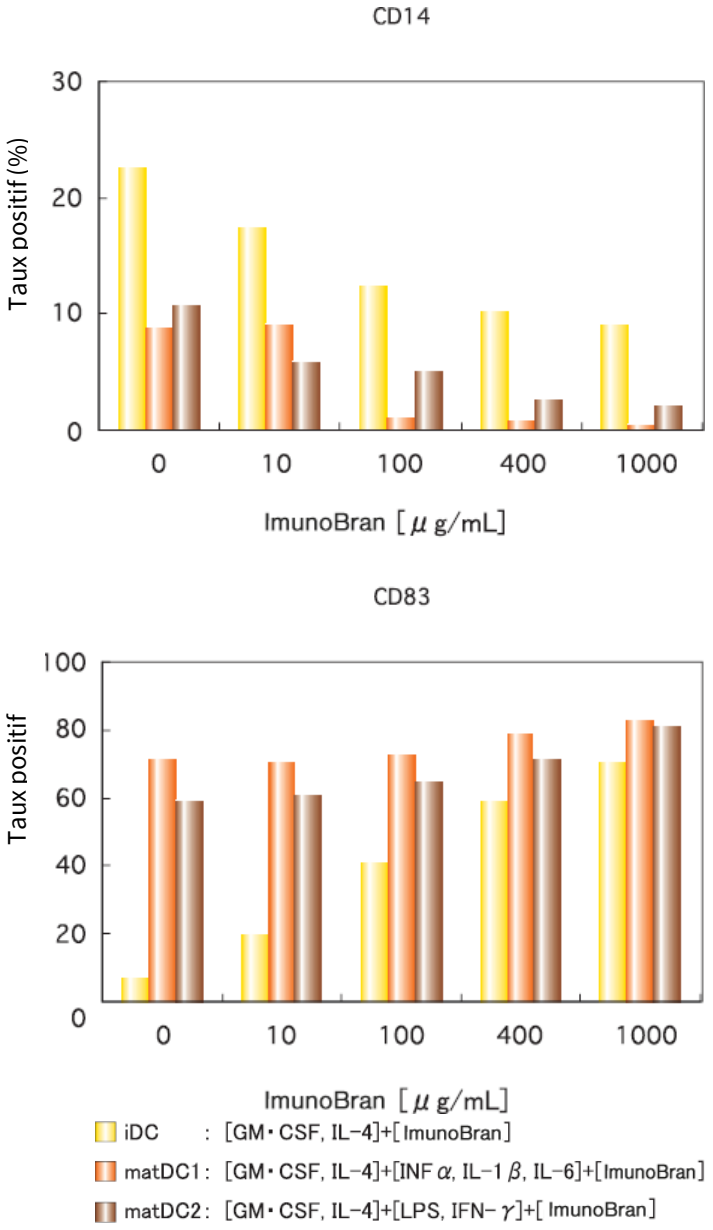
8.1.4. Soutien à la différenciation des cellules dendritiques

Des monocytes qui ont été ensuite cultivés pendant 6 jours en présence de GM-CSF et IL-4 en vue de préparer des cellules dendritiques immatures (iDC) ont été isolés du sang périphérique de sujets en bonne santé. Le septième jour, de l'ImunoBran de différentes concentrations a été ajouté aux cellules dendritiques immatures. La maturation des cellules dendritiques a été observée pendant les deux jours de leur incubation. Nous avons effectué une opération identique en utilisant deux sortes de médiums de culture ayant un effet de soutien à la transformation des cellules iDC en cellules dendritiques matures appelées matDC1, voire matDC2. Dans les cellules dendritiques immatures (iDC), l'ImunoBran a inhibé, en fonction des doses, l'expression du marqueur des monocytes CD14 et a accru celle du marqueur des cellules dendritiques CD83. Ce résultat indique que l'ImunoBran contribue à la différenciation des cellules dendritiques.

Soutien de la différenciation des cellules dendritiques par l'ImunoBran



Cholujova D. et coll., „Augmentation de la maturation des monocytes humains dérivés de cellules dendritiques grâce à ImunoBran", NEOPLASMA, 56, 2, 2009

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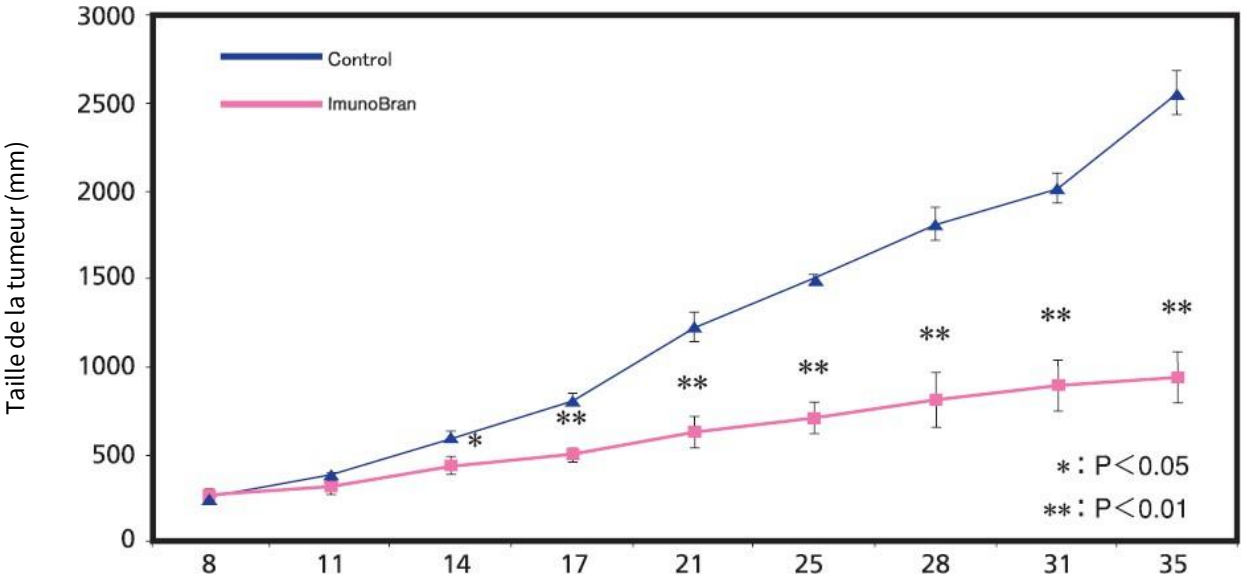
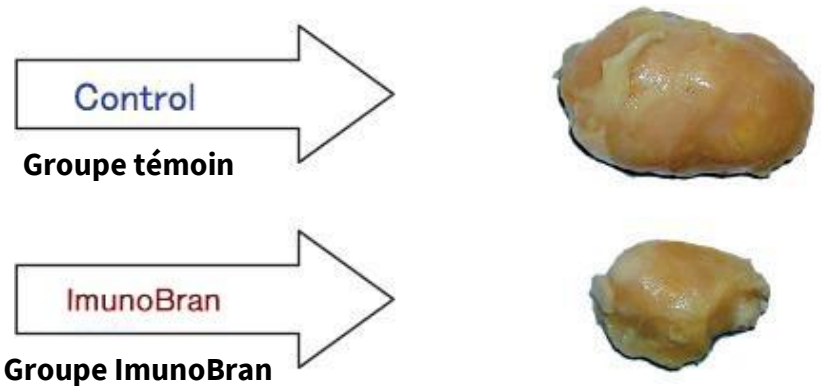
8.1.5. Effet anticancéreux de l'ImunoBran

On a injecté dans la région fémorale droite de souris blanches femelles suisses une dose de $2,5\times10^6$ de cellules de carcinome ascitique d'Ehrlich (abrév. angl. EAC) et la taille de la tumeur a été observée pendant les jours suivants, à partir du 8e jour suivant l'injection jusqu'au 35e jour.
On a administré un tampon phosphate salin (abrév. angl. PBS) au groupe témoin des souris et 40 mg/kg de l'ImunoBran au groupe ciblé par voie intrapéritonéale trois fois par semaine pendant trois semaines à partir du 8e jour suivant l'injection d'EAC. Ensuite, après le traitement, la taille de la tumeur est mesurée. Dans le groupe ImunoBran une inhibition beaucoup plus importante de la croissance de la tumeur a été constatée le 14e jour après l'injection d'EAC par rapport au groupe. Les images de la tumeur du 35e jour montrent même une régression de la tumeur dans le groupe ImunoBran.

Effet anticancéreux de l'ImunoBran In-vivo





Ghoneum M. et coll., „L'arabinoxylane modifié de son de riz (MGN-3/ImunoBran) améliore l'activité éradicatrice intracellulaire des cellules phagocytoses humaines in vitro", Nutrition and Cancer, 2008

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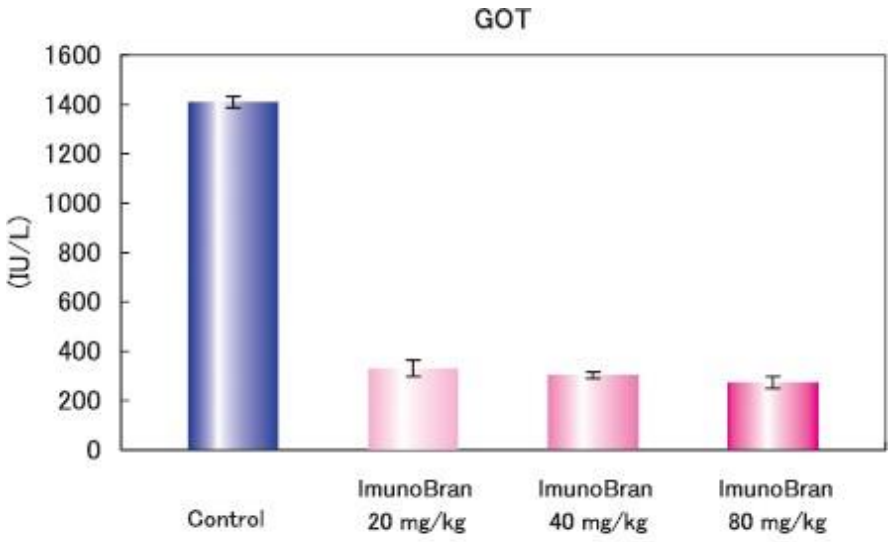
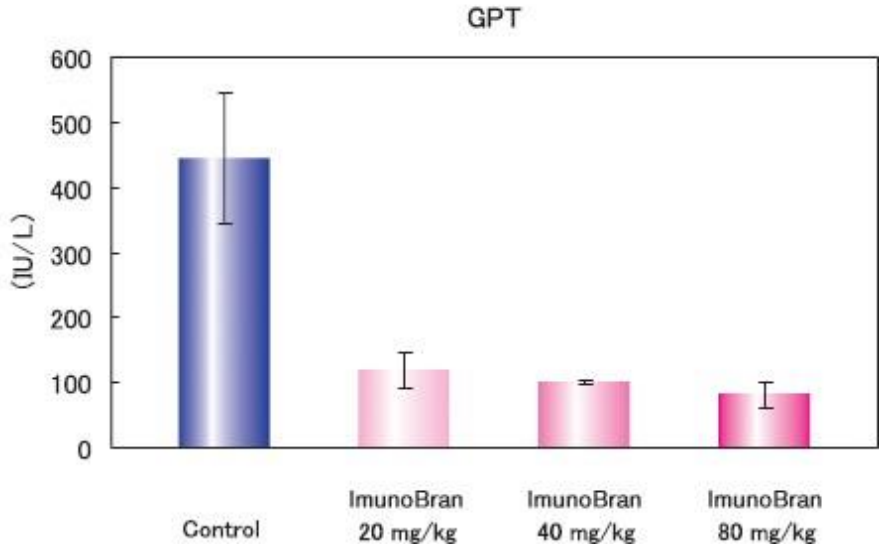
8.2. Effet anti-inflammatoire

8.2.1 Influence sur l'altération du foie

Dans le but de provoquer une altération de leur foie, une injection de 800 mg/kg de D-galactosamine a été réalisée par voie intrapéritonéale sur des rats mâles Wistar (5 individus par groupe). Vingt-quatre heures après l'injection de la D-galactosamine on a suivi les valeurs GOT et GPT dans le sérum indicateur de l'altération du foie. Une heure après l'administration de la D-galactosamine, l'ImunoBran leur a été appliqué par voie intrapéritonéale sous un dosage de 20, 40, 80 mg/kg. Les valeurs GOT et GPT dans le sérum du groupe témoin sans ImunoBran étaient, 24 heures après l'administration de la D-galactosamine, de l'ordre de 1410 IU/l et 445 IU/l. Les valeurs GOT et GPT du sérum des groupes soignés à l'aide de l'ImunoBran étaient, comparativement à ces valeurs-là et dans le cas des trois dosages, bien inférieures.





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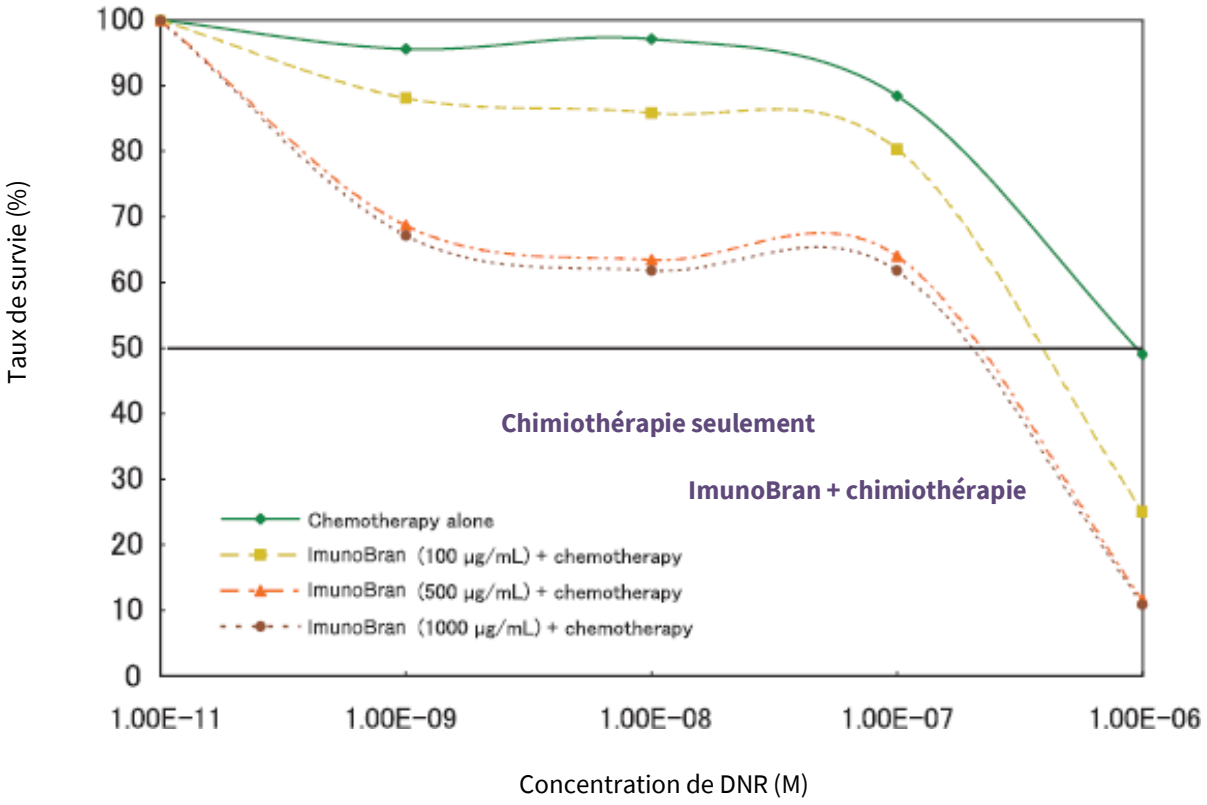
8.2.2. Traitement combiné avec médicaments chimio thérapeutiques

Des cellules tumorales mammaires humaines (MCF-7) (au nombre de 1×10^4 cellules) ont été incubées in vitro durant 3 jours avec différentes concentrations de l'ImunoBran et de daunorubicine, médicament chimio thérapeutique (DNR). Pour le calcul des cellules viables, on a eu recours à l'analyse MTT par laquelle on a par ailleurs établi la concentration de DNR qui réduit le nombre des cellules cancéreuses viables exactement de moitié (IC_{50}). La DNR a inhibé la survie des cellules MCF-7 en fonction de la concentration, sachant que la valeur IC_{50} représentait une concentration de 1µM. Quand les cellules MCF-7 ont été cultivées avec la DNR et l'ImunoBran, la valeur IC_{50} a baissé fortement (la valeur IC_{50} représentait une concentration de 0,2µM).

Changements de la sensibilité des cellules MCF-7 à la DNR liés à l'administration simultanée de l'ImunoBran



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8.2.3. Amélioration de la qualité de vie

Effet de l'ImunoBran sur la survie et amélioration de la qualité de vie des patients en stade progressif de cancer

Deux cent cinq patients souffrant de tumeurs malignes et subissant un traitement aux médicaments alternatifs et chimio thérapeutiques avec des réactions défavorables modérées ont été répartis en deux groupes. Un traitement conventionnel alternatif et chimio thérapeutique a été administré au groupe témoin; le groupe ImunoBran, outre une thérapie identique à celle du groupe témoin, a obtenu en plus 1 g de l'ImunoBran trois fois par jour après les repas pendant 18 mois. On a ensuite examiné la corrélation entre l'activité mesurée des cellules NK pendant la période suivie et le taux de survie.
Afin d'évaluer la qualité de vie des patients, deux échelles ont été créées – une de 0 à 4 pour l'appréciation du niveau de « douleurs », de la « fatigue » et des « nausées », et une autre de 0 à 3 pour l'appréciation de « l'appétit », sachant que les patients jugeaient les différents paramètres au début et à la fin de la période suivie. Sur les 205 participants à l'étude, 53 patients du groupe témoin n'ont pas pu poursuivre le traitement conventionnel alternatif et ont été éliminés de l'étude, et ce sont donc en fin de compte 152 patients qui ont été évalués et analysés (56 du groupe témoin et 96 du groupe ImunoBran). Le taux de survie en fin de période suivie dans le groupe témoin et dans le groupe de l'ImunoBran ont été respectivement de 35,8 % et de 54,2 %. Ceci représente un taux de 50 % supérieur de survie au profit du groupe ImunoBran par rapport à celui du groupe témoin. L'étude a mis en évidence une corrélation entre une activité des cellules NK accrue et un taux de survie supérieur (Tableau n° 1). L'étude a démontré également que la qualité de vie en fin de période suivie s'est améliorée comparativement à l'état en début d'étude dans les deux groupes, témoin et l'ImunoBran; l'amélioration de l'appétit surtout, dans le groupe ImunoBran, est remarquable (Tableau n° 2).

Tableau n° 1 : taux de survie et activité des cellules NK

	Groupe ImunoBran	**Groupe témoin**
Taux de survie	52/96 (54,2 %)	19/56 (35,8 %)
Activité des cellules NK		
<19,9 %	17/40 (42,5 %)**	2/16 (12,5 %)
20~40 %	18/35 (51,4 %)*	7/25 (28,0 %)
≥40 %	17/21 (81,0 %)	10/15 (66,7 %)

**: p<0,01 *: p <0,05

Tableau n° 2 : Amélioration de la qualité de vie

Qualité de vie	**douleurs**			**fatigue**			**nausées**			**appétit**		
	Avant	Après	%	Avant	Après	%	Avant	Après	%	Avant	Après	%
Groupe témoin	2,9	2,5	-14,0	3,5	2,9	-17,1	2,5	2,9	-14,6	1,6	1,9	+15,9
Groupe ImunoBran	2,2	1,9	-15,9	2,9	2,4	-17,3	2,3	2,0	-13,3	1,7	2,1	+24,2

(-): indique la baisse des facteurs négatifs (douleurs, fatigue et nausées)
(+): indique l'amélioration de l'appétit

Takahara K. et coll. „Effet de l'arabinoxylane dérivé du son de riz (MGN-3, ImunoBran) sur la prolongation de la vie et l'amélioration de sa qualité chez les patients en stade progressif du cancer. "Clinical Pharmacology and Therapy, 2004

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9. RÉFÉRENCES (ImunoBran® = BioBran®)

9.1. Recherche académique et articles sur le produit ImunoBran MGN-3

2023 Biobran/ImunoBran/MGN-3, an Arabinoxylan Rice Bran, Protects against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An In Vitro and In Silico Study *Mamdooh Ghoneum, Shaymaa Abdulmalek and Hewida H. Fadel*

Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19), poses a serious global public health threat for which there is currently no satisfactory treatment. This study examines the efficacy of Biobran/MGN-3 against SARS-CoV-2. Biobran is an arabinoxylan rice bran that has been shown to significantly inhibit the related influenza virus in geriatric subjects. Here, Biobran's anti-SARS-CoV-2 activity was assessed using MTT and plaque reduction assays, RT-PCR, ELISA techniques, and measurements of SARS-CoV-2-related gene expression and protein levels. For Vero E6 cells infected with SARS-CoV-2, Biobran reduced the viral load by 91.9% at a dose of 100 µg/mL, it reduced viral counts (PFU/mL) by 90.6% at 50 µg/mL, and it exhibited a significant selectivity index (EC50/IC50) of 22.5. In addition, Biobran at 10 µg/mL inhibited papain-like proteinase (PLpro) by 87% and ACE2 SARS-CoV-2 Sprotein RBD by 90.5%, and it significantly suppressed SARS-CoV-2 gene expression, down-regulating E-gene and RdRp gene expression by 93% each at a dose of 50 µg/mL and inhibiting the E-protein by 91.3%. An in silico docking study was also performed to examine the protein–protein interaction (PPI) between SARS-CoV-2 RBD and DC-SIGN as well as between serine carboxypeptidase and papain-like protease PLpro. Serine carboxypeptidase, an active ingredient in Biobran, was found to interfere with the binding of SARS-CoV-2 to its receptor DC-SIGN on Vero cells, thus preventing the cell entry of SARS-CoV-2. In addition, it impairs the viral replication cycle by binding to PLpro. We conclude that Biobran possesses potent antiviral activity against SARS-CoV-2 in vitro and suggest that Biobran may be able to prevent SARS-CoV-2 infection. This warrants further investigation in clinical trials.

2022 Enhancing effect of streptozotocin-induced insulin deficit on antitumor innate immune defense in rats

Hajto Tibor, Péczely László, Kuzma Monika, Hormay Edina, Ollmann Tamás, Jaksó Pál, Baranyai Lilla and Karádi Zoltán

Background: There are conflicting data about the relationship between diabetes mellitus and cancer risk in that growing evidence suggest a possible role of endogenous elevated insulin level which is often found in Non-Insulin-Dependent-Diabetes-Mellitus or an exogenous hyperinsulinemia observed often in Insulin-Dependent-Diabetes-Mellitus. In the last years higher attention focused on the role of immunoregulation both in the insulin production by β-cell of Langerhans-islets and in the insulin sensitivity (resistance) of insulin receptors. Interestingly, cytokines from type-2 innate immune cells, such as M2 macrophages or D2 dendritic cells exhibit a protective effect on both types of diabetes. However, the effect of insulin on the balance between type-1 and type-2 natural immune mechanisms, which is important for the tumour defence, was poorly investigated. Material and methods: Streptozotocin (STX)-treated Wister rats was treated per oral with a non-optimal single dose of an evidence based and standardized plant immunomodulator, namely Rice Bran Arabinoxylan Concentrate (RBAC) which has been shown to activate type-1 innate immune cells (such as M1, D1 and NK cells). 24h after a single dose of RBAC (45mg/kg) four parameters of NK cells were determined with flow cytometry using stained CD161-APC and CD314-PE monoclonal antibodies and by haematological examinations. The results were compared with negative controls (without STX or RBAC treatment). Results: Since STX caused a significantly reduced lymphocyte production in bone marrow, only the RBAC-induced relative increases in number of NKR-P1+ and LGL cells among the all-lymphocyte population parallel with the frequency and intensity of the most important Killing Activator Receptor, namely NKG2D among the total NK cell population were determined. In the STX-untreated group RBAC induced only not significant increases compared with negative control values. However, in STX-treated groups all four NK parameters revealed RBAC-induced significant increases ($p<0.05$) compared to the negative controls. Conclusion: These results suggest the hypothesis that insulin deficit can increase the immunomodulator-induced activation of type-1 innate immune cells indicating that insulin takes part on regulation of the natural immune balance inhibiting the type-1 innate antitumor defence.

2022 Impact of Ingestion of Rice Bran and Shitake Mushroom Extract on Lymphocyte Function and Cytokine Production in Healthy Rats *Scott Giese, BS George Richard Sabell, BS, Mary Coussons-Read, PhD*

ABSTRACT: This article provides a controlled evaluation of the ability of dietary supplementation with a commercially available rice bran extract modified with shitake mushroom extract (MGN-3) to support the immune function by assessing the ability of immunocytes to proliferate and produce cytokines in response to a mitogenic challenge. Twenty-four male Lewis rats were fed a control diet (Maypo sweetened oatmeal) or Maypo containing the recommended daily dose of MGN-3 for 2 weeks. This treatment modestly enhanced mitogen enhanced proliferation of splenocytes and interferon-gamma (IFN-g) production, and significantly increased proliferation of splenocytes to the superantigen toxic shock syndrome toxin-1 (TSST-1) as well as natural killer (NK) cell activity and production of interleukin-2 (IL-2) by stimulated lymphocytes. These data support the contention that ingestion of MGN-3 can support immune cell function. These data add to a growing body of data showing that ingestion of MGN-3 improves the ability of immune cells to proliferate the lyse tumour cells, suggesting that it may have utility as a dietary aid to support the immune system.

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2021 Clinical Cancer Strategy (Clinical Review) *Serge Jurasunas*
This clinical cancer strategy incorporates advancements in cancer treatment based on a multi-approach to the disease that includes targeting apoptosis, immune cell activation, angiogenesis, restoration of cellular respiration, inhibition of inflammatory mediators, not mentioning some secondary factors such as intoxication, disturbed microbiome, and nervous disorders. I believe that a real breakthrough in cancer needs to promote immune system enhancement and activate apoptosis. These two important mechanisms of approaching cancer, principally through the clinical application of the P53 tumour suppressor gene and other apoptotic players that for the past 15 years have been included in my cancer strategy as a diagnostic, prognosis, and follow up treatment. P53 mutation or mutated P53 protein remains the essential factor when it comes to treating cancer either from conventional therapy or an alternative approach or in combination.

2021 Dieatary Supplementation with BioBran-MGN-3 Increases Innate Resistance and Reduces the Incidence of Influenza-like Illnesses s in Elderly Subjects: A Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Trial
Ahmed F. Elsaid , Sudhanshu Agrawal , Anshu Agrawal and Mamdooh Ghoneum PEER REVIEWED
Abstract: Influenza-like illness (ILI) remains a major cause of severe mortality and morbidity in the elderly. Aging is associated with a decreased ability to sense pathogens and mount effective innate and adaptive immune responses, thus mandating the development of protective nutraceuticals. Biobran/MGN-3, an arabinoxylan from rice bran, has potent anti-aging and immunomodulatory effects, suggesting that it may be effective against ILI. The objective of the current study was to investigate the effect of Biobran/MGN-3 on ILI incidence, natural killer (NK) cell activity, and the expressions of RIG-1 (retinoic acid-inducible gene 1), MDA5 (melanoma differentiation-associated protein 5), and their downstream signalling genes ISG-15 (interferon-stimulated genes 15) and MX1 (myxovirus (influenza) resistance 1, interferon-inducible). A double-blind, placebo-controlled clinical trial included eighty healthy older adults over 55 years old, 40 males and 40 females, who received either a placebo or Biobran/MGN-3 (500 mg/day) for 3 months during known ILI seasonality (peak incidence) in Egypt. The incidence of ILI was confirmed clinically according to the WHO case definition criteria. Hematological, hepatic, and renal parameters were assessed in all subjects, while the activity of NK and NKT (natural killer T) cells was assessed in six randomly chosen subjects in each group by the degranulation assay. The effect of Biobran/MGN-3 on RIG-1 and MDA5, as well as downstream ISG15 and MX1, was assessed in BEAS-2B pulmonary epithelial cells using flow cytometry. The incidence rate and incidence density of ILI in the Biobran/MGN-3 group were 5.0% and 0.57 cases per 1000 person-days, respectively, compared to 22.5% and 2.95 cases per 1000 person-days in the placebo group. Furthermore, Biobran/MGN-3 ingestion significantly enhanced NK activity compared to the basal levels and to the placebo group. In addition, Biobran/MGN-3 significantly upregulated the expression levels of RIG-1, MDA5, ISG15, and MX1 in the human pulmonary epithelial BEAS-2B cell lines. No side effects were observed. Taken together, Biobran/MGN-3 supplementation enhanced the innate immune response of elderly subjects by upregulating the NK activity associated with reduction of ILI incidence. It also upregulated the intracellular RIG-1, MDA5, ISG15, and MX1 expression in pulmonary epithelial tissue cultures. Biobran/MGN-3 could be a novel agent with prophylactic effects against a wide spectrum of respiratory viral infections that warrants further investigation.

2020 Arabinoxylan rice bran (MGN-3/Biobran) alleviates radiation-induced intestinal barrier dysfunction of mice in a mitochondrion-dependent manner *Zhenguo Zhaoa , Wei Chengb , Wei Quc , Kai Wangd* PEER REVIEWED
MGN-3 is an arabinoxylan from rice bran that has been shown to be an excellent antioxidant and radioprotector. This study examined the protective effects of MGN-3 on radiation-induced intestinal injury. Mice were treated with MGN-3 prior to irradiation, then continued to receive MGN-3 for 4 weeks thereafter. MGN-3 increased the activity of mitochondrial respiratory chain complexes Ⅰ, Ⅲ, Ⅳ and Ⅴ, the intercellular ATP content, the mitochondria-encoded gene expression and mitochondrial copy numbers in the jejunal and colonic mucosa. MGN-3 reduced the oxidative stress levels and inflammatory response indicators in the serum and jejunal and colonic mucosa. Antioxidant indicators such as superoxide dismutase, glutathione peroxidase, catalase and total antioxidant capacity were significantly increased in the serum and jejunal and colonic mucosa in the MGN-3 group. Moreover, MGN-3 decreased the gene abundances and enzymatic activities of caspase-3, 8, 9 and 10 in the jejunal and colonic mucosa. The endotoxin, diamine peroxidase, D-lactate and zonulin levels were significantly reduced in the serum and jejunal and colonic mucosa in the MGN-3 group. MGN-3 also markedly upregulated the gene abundances of ZO-1, occluding, claudin-1 and mucin 2. MGN-3 effectively attenuated radiation-induced changes in the intestinal epithelial mitochondrial function, oxidative stress, inflammatory response, apoptosis, intestinal permeability, and barrier function in mice. These findings add to our understanding of the potential mechanisms by which MGN-3 alleviates radioactive intestinal injury.

2020 Chemopreventive role of arabinoxylan rice bran, MGN-3/Biobran, on liver carcinogenesis in rats
Nariman K. Badr El-Din, Doaa A. Ali, Reem Othman, Samuel W. French, Mamdooh Ghoneum PEER REVIEWED
Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and one of the most lethal. MGN-3/Biobran is a natural product derived from rice bran hemicelluloses and has been reported to possess a potent anticancer effect in a clinical study of patients with HCC. The current study examines the mechanisms by which Biobran protects against chemically induced hepatocarcinogenesis in rats. The chemical carcinogen used in this study is N-nitrosodiethylamine (NDEA) plus carbon tetrachloride (CCl4). Rats were treated with this carcinogen, and the animals were pre-treated or post treated with Biobran via intraperitoneal injections until the end of the experiment. Treatment with Biobran resulted in: 1) significant alleviation of liver preneoplastic lesions towards normal hepatocellular architecture in association with inhibition of collagen fibre deposition; 2) arrest of cancer cells in the sub-G1 phase of the cell cycle; 3) increased DNA fragmentation in cancer cells; 4) down-regulated expression of Bcl-2 and up-regulated expression of p53, Bax, and caspase-3; and 5) protection against carcinogen-induced suppression of IkappaB-alpha (IκB-α) mRNA expression and inhibition of nuclear factor kappa-B (NF-κB/p65) expression. Additionally, the effect of Biobran treatment was found to be more significant when supplemented prior to carcinogen-induced hepatocarcinogenesis as compared to posttreatment. We conclude that Biobran inhibits hepatocarcinogenesis in rats by

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mechanisms that include induction of apoptosis, inhibition of inflammation, and suppression of cancer cell proliferation. Biobran may be a promising chemopreventive and chemotherapeutic agent for liver carcinogenesis.

2020 Un immunomodulateur™ végétal standardisé, fondé sur les faits (composé d'arabinoxylane de son de riz) peut-il accroître les effets de la gemcitabine de façon synergique? Étude de cas sur un patient présentant un carcinome canalaire du pancréas *Tibor Hajto* Université de Médecine de Pecs, Hongrie*

Contexte: Le carcinome canalaire du pancréas est l'une des principales causes de mortalité par cancer. Associée au nab-paclitaxel lors d'un traitement standard de première intention, la gemcitabine aboutit à une amélioration des paramètres cliniques qui reste transitoire. Les observations immunologiques indiquent qu'un dérèglement immunitaire induit par la tumeur peut jouer un rôle dans cette résistance rapide. Il a été démontré que les cellules immunitaires innées de type 2 activent diverses cellules régulatrices inhibitrices et facteurs de croissance pouvant diminuer à la fois l'activité des effecteurs et la sensibilité immunitaire des cellules tumorales. On sait que la sensibilité immunitaire est liée aux molécules induites par le stress A et B du CMH-I (MICA et MICB) sur les cellules tumorales, plus importants ligands du récepteur d'activation des cellules NK (NKG2D). L'amélioration de l'expression des molécules MICA et MICB sur les cellules tumorales grâce à la gemcitabine ayant été découverte il y a quelques années, l'utilisation de cette dernière associée à un immunomodulateur™ fondé sur les faits suscite un intérêt clinique croissant.

Matériels et méthodes: Cette étude décrit le cas d'un patient présentant un adécarcinome canalaire pancréatique métastasé et inopérable, traité à la gemcitabine (1678 mg) et au nab-paclitaxel (210 mg) les jours 1, 8 et 15 de chaque mois durant huit cycles. Ce traitement a été régulièrement combiné à 45 mg/kg de Biobran/MGN-3 (composé d'arabinoxylane de son de riz standardisé) administré par voie orale trois fois par semaine.

Résultats: Patient âgé de 56 ans, adécarcinome canalaire inopérable (39 x 46 mm) situé dans la partie caudale du pancréas et multiples métastases hépatiques (10-30 mm) décelés par scanner et biopsie. Patient quasiment en phase terminale (perte de 27 kg de masse corporelle et douleurs intenses). Trois mois après le début du traitement, le scanner a permis d'observer une rémission de la tumeur pancréatique (25 x 38 mm) et une réduction des métastases hépatiques (de 3 à 10 mm en moyenne). Sept mois plus tard, une rémission totale au niveau du pancréas et une diminution supplémentaire de 3 à 6 mm des métastases hépatiques ont été constatées. Ces rémissions ont également été établies après 10 mois. Le patient ne se plaint d'aucune gêne et est capable de travailler à 100 %.

Conclusions: L'association de gemcitabine et d'immunomodulateur™ s fondés sur les faits et standardisés (tels que le MGN-3) peut ouvrir de nouvelles voies dans le domaine du traitement des tumeurs.

2020 The Immunomodulating Effects of Arabinoxylan Rice Bran (Lentin) on Hematologic Profile, Nutritional Status and Quality of Life among Head and Neck Carcinoma Patients Undergoing Radiation Therapy: A Double Blind Randomized Control Trial 2nd place, Philippine College of Radiology Research Contest, Oral Presentation PEER REVIEWED

Dorothy Faye S. Tan, MD; Jerickson Abbie S. Flores, MD Jose R. Reyes Memorial Medical Center

Immunostimulants have been explored to reduce the complications of radiation/chemotherapy. This double blind randomized trial aimed to determine the immunomodulating effects of Lentin among head and neck cancer patients in addressing radiation treatment complications such as anaemia, leukopenia, weight loss and improvement of quality of life. Sixty-five (65) patients were enrolled and given either Lentin or placebo - 2 weeks prior, during radiation/chemoradiotherapy and 2 months after. Complete Blood Count, Body Mass Index, percent weight loss and EORTC Quality of Life questionnaires QLQ H&N35 were used to assess the degree of anaemia, weight loss and quality of life. Overall CBC results revealed higher values on all parameters in Lentin arm. Upon completion of radiochemotherapy, the Lentin arm showed significantly higher mean hemoglobin by 1.30 g/dL (p=0.010), hematocrit (p=0.001), RBC (p=0.001) and platelets (p=0.017). Also, higher overall BMI (22.69 versus 21.52) and a lower percent weight loss (6.10% versus 6.91%) for Lentin compared to placebo were noted with p-values of 0.199 and 0.571, respectively. Treatment related toxicity using the RTOG grading showed lower severity scores on all parameters (p-values: >0.05) and better QoL scores for patients taking Lentin (p-value: 0.019). Results from this study showed better clinical outcomes for patients taking Lentin. These have led to fewer blood transfusions, treatment delays and hospital admissions, avoidance of treatment mortalities and morbidities, and improved quality of life among head and neck cancer patients undergoing chemoradiotherapy

2019 Arabinoxylan rice bran (MGN-3/Biobran) enhances radiotherapy in animals bearing Ehrlich ascites carcinoma

Nariman K. Badr El-Din,, Said K. Areida , Kvan O. Ahmed and Mamdooh Ghoneum*

This study examines the ability of arabinoxylan rice bran (MGN-3/Biobran) to enhance the anti-cancer effects of fractionated X-ray irradiation of Ehrlich solid tumor-bearing mice. Swiss albino mice bearing tumors were exposed to the following: (i) Biobran treatment (40 mg/kg/day, intraperitoneal injections) beginning on day 11 post-tumor cell inoculation until day 30; (ii) ionizing radiation (Rad) 2 Gy at three consecutive doses on days 12, 14 and 16; or (iii) Biobran + Rad. Final tumor weight was suppressed by 46% for Biobran, 31% for Rad and 57% for the combined treatment (Biobran + Rad) relative to control untreated mice. Biobran and Rad also arrested the hypodiploid cells in the sub-G1-phase, signifying apoptosis by +102% and +85%, respectively, while the combined treatment induced apoptosis by +123%, with similar results in the degree of DNA fragmentation. Furthermore, Biobran + Rad upregulated the relative gene expression and protein level of p53 and Bax in tumor cells, down-regulated Bcl-2 expression, and increased the Bax/Bcl-2 ratio and caspase-3 activity, with the combined treatment greater than for either treatment alone. Additionally, the combined treatment modulated the decrease in body weight, the increase in liver and spleen weight, and the elevation of liver enzymes aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transferase to be within normal values. We conclude that Biobran enhances radiation therapy-induced tumor regression by potentiating apoptosis and minimizing toxicities related to radiation therapy, suggesting that Biobran may be useful in human cancer patients undergoing radiotherapy and warranting clinical trials.

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2019 The enhancing efects of Biobran/MGN-3, an arabinoxylan rice bran, on healthy old adults' health-related quality of life: a randomized, double-blind, placebo-controlled clinical trial *A. F. Elsaid1 · R. M. Fahmi2 · M. Shaheen3 · M. Ghoneum*
Purpose The world's older population is growing rapidly and the need to find measures to combat age-associated decline of physical, mental, and cognitive functions and improve their health-related quality of life (HRQOL) is escalating. Biobran/ MGN-3, an arabinoxylan rice bran, has been previously reported to improve the quality of life in cancer patients. The objective of the current study was to examine the effect of a low dose of Biobran/MGN-3 supplementation on the HRQOL in a healthy older adult population. Methods Sixty apparently healthy subjects, 40 males and 20 females, over 56 years old were recruited and blindly randomized into two group receiving either placebo or Biobran/MGN-3 (250 mg/day for 3 months). Participants did not take any vitamins or medications during the study and their health was closely monitored. HRQOL was assessed at the initiation and termination of the study using the previously validated Arabic version of SF-12v2 questionnaire. Results For all measured HRQOL domains, there was no statistically significant difference in baseline scores between the two groups. Compared to baseline values and placebo-treated subjects, Biobran/MGN-3 supplementation significantly enhanced the levels of physical and mental component summary scores as well as role-physical, bodily pain, vitality, and social functioning subdomain scores. Conclusion these results show that Biobran/MGN-3 is a promising psychoneuroimmune modulatory agent that could improve the HRQOL in healthy old adults.

2018 The Effect of a Hydrolyzed Polysaccharide Dietary Supplement on Biomarkers in Adults with Nonalcoholic Fatty Liver Disease *John E. Lewis , Steven E. Atlas, Oscar L. Higuera, Andrea Fiallo, Ammar Rasul, Ashar Farooqi, Olga Kromo, Laura A. Lantigua, Eduard Tiozzo , Judi M. Woolger, Sharon Goldberg, Armando Mendez , Allan E. Rodriguez, and Janet Konefal*
The primary objective of the study was to evaluate the effect of a hydrolysed polysaccharide, Rice Bran Arabinoxylan Compound (RBAC), on biomarkers in adults with non-alcoholic fatty liver disease (NAFLD). A 90-day randomized double-blind placebo-controlled trial examined the effect of RBAC on complete blood count, liver enzymes, lipids, oxidative stress markers, cytokines, and growth factors. Twenty-three adults with NAFLD were enrolled and randomly assigned to one of the two study conditions (n = 12 RBAC and n = 11 placebo) and consumed 1 gram/day of either compound for 90 days. Subjects were assessed at baseline and 45 and 90 days. No adverse effects were reported. Alkaline phosphatase significantly decreased (−3.1%; SD = 19.9; F[1, 19] = 5.1, p = 0.03) in the RBAC group compared to placebo. Percent monocytes (17.9%; SD = 18.3; F[1, 19] = 5.9, p = 0.02) and percent eosinophils (30.6%; SD = 30.5; F[1, 19] = 12.3, p < 0.01) increased in the RBAC group. IFN-γ (156%; SD = 131.8; F[1, 19] = 4.2, p = 0.06) and IL-18 (29.1%; SD = 64; F[1, 19] = 5.3, p = 0.03) increased in the RBAC group compared to placebo. Other improvements were noted for platelets, neutrophils, neutrophil-lymphocyte ratio, γ-glutamyl transferase, and 4-hydroxynonenal. RBAC had beneficial effects on several biomarkers that add to the known immunomodulatory activities of RBAC, which may be promising for people with NAFLD.

2018 New Perspectives to Improve the MHC-I Unrestricted Immune Mechanisms against Malignant Tumors *Tibor Hajto* Since malignant tumours parallel with their progression can lose their sensitivity against the MHC-I restricted T lymphocytes because of their escape in tumour antigen presenting, we need immunomodulators which are able to activate MHC-I unrestricted tumoricidal mechanisms of innate immune system. In contrast to the adaptive system, the innate immune cells have regularly a basic activity (priming) which can determine their function ability and render possible a polarity similar to neuroendocrine system. Namely, innate immune cells are committed in two directions. Type-1 cells involve tumoricidal cascade mechanisms which activate the MHC-I unrestricted killer cells (such as NK-cells) and Type-2 cells activate cell proliferation by production of Growth Factors (GFs), affect chronic inflammation, stimulate the angiogenesis and inhibit the type-1 system. As shown in this paper the activity of type 1 cells is down regulated parallel with the tumour progression and available information suggest a regular tumour-induced dominance of type-2 cells. Immunomodulators must improve this disturbed balance. Type-1 natural cells can be activated only via stimulation of phagocytic cells by PAMP like structures which have always a natural origin and the chemistry is not able to produce them. In the tumoricidal activity of MHC-I unrestricted killer cells the expression of NKG2D receptors and the expression of their stress related ligands (MICA/B, UBPL1-3) have pivotal regulatory role generating the kill signal. The aim of this review paper to support hypotheses as to whether an increase in expression of KAR on MHC-I unrestricted killer cells by evidence based plant immunomodulators and parallel stimulating the expression of stress related ligands on tumour cells by GFR inhibitors or cytostatic drugs (such as Gemcitabin) can result in clinical benefits. Case reports using standardized Rice Bran Arabinoxylan Concentrate (Biobran/MGN-3) in combination with GFR inhibitors or Gemcitabin show astonishing clinical responses. Unfortunately, in spite of clinical and immunological evidences this plant immunomodulator is registered only as food supplements and a further research of these hypotheses is therefore hindered.

2018 The Novel Effects of a Hydrolyzed Polysaccharide Dietary Supplement on Immune, Hepatic, and Renal Function in Adults with HIV in a Randomized, Double-Blind Placebo-Control Trial *John E. Lewis, Steven E. Atlas, Muhammad H. Abbas, Ammar Rasul, Ashar Farooqi, Laura A. Lantigua, Frederick Michaud, Sharon Goldberg, Lucas C. Lages, Oscar L. Higuera, Andrea Fiallo, Eduard Tiozzo, Judi M. Woolger, Stephanie Ciraula, Armando Mendez, Allan Rodriguez & Janet Konefal*
The primary objective of the study was to evaluate the effects of a hydrolysed polysaccharide, rice bran arabinoxylan compound (RBAC), on immune, hepatic, and renal function in HIV þ individuals. A six-month randomized double-blind placebo-controlled trial was utilized to conduct the intervention. Forty-seven HIV þ participants on stable antiretroviral therapy were enrolled and randomly assigned to one of the two study conditions (n ¼ 22 RBAC and n ¼ 25 placebo) and consumed 3 gram/day of either compound for six months. Participants were assessed at baseline and 3 and 6 months follow-up for CD4þ and CD8þ, liver enzymes, and kidney function. No side effects were reported, and liver and kidney markers nearly remained completely within normal limits. The percentage change in CD4þ was similar for the placebo (þ2.2%) and RBAC (þ3.1%) groups at 6 months follow-up. The percentage change in CD8þ count significantly decreased from baseline to 6 months in the RBAC group(-5.2%), whereas it increased in the placebo group (þ57.8%; p ¼ 0.04). The CD4þ/CD8þ ratio improved clinically in the RBAC group from 0.95 (SD

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1⁄40.62) at baseline to 1.07 (SD 1⁄40.11) at 6 months, whereas it declined in the placebo group from 0.96 (SD 1⁄40.80) at baseline to 0.72 (SD 1⁄40.59) at 6 months. Our results showed a statistically significant decrease in CD8þ count and a clinically significant increase in CD4þ/CD8þ ratio for the RBAC group compared to the placebo group. Thus, the results of this study suggest that the immunomodulatory and antisenescent activities of RBAC are promising for the HIV population.

2017 Urgent Necessity for Standardized and Evidence Based Plant Immunomodulators (Such As Rice Bran Arabinoxylan Concentrate/MGN-3) for the Tumor Research *Tibor Hajto*

Biological targeting therapies can inhibit the cascade of cell proliferation and enhance the sensitivity of malignant tumour cells against natural immune effector cells. Clinical observations suggest that their combination with evidence based and standardized plant immunomodulators (such as arabinoxylan concentrate using Biobran/MGN-3) can induce astonishing results. Since the escape of tumour cells from T lymphocytes is well known, growing interest is focusing on the Pathogenic Associated Molecular Pattern (PAMP) molecules which are able to stimulate the so called type-1 natural antitumor mechanisms in a MHC unrestricted manner. However, PAMP molecules exist only in the nature (bacteria and plants). The chemistry is not able to produce them. Bacteria are toxic. Therefore growing interest developed for the PAMP like molecules in the plants. Unfortunately, in terms of PAMP like molecules standardized plant immunomodulators (such as arabinoxylan concentrate in Biobran/MGN-3) are registered world over as food supplement and therefore their further clinical research in various oncological centres is inhibited.

2017 Can a standardized plant immunomodulator (rice bran arabinoxylan concentrate/MGN-3) increase the effects of MEK and BRAF inhibitors with clinical benefit? Case report of a patient with carcinoma in biliary duct *Tibor Hajto*

Background: Targeting hyperactive mitogen-activated protein kinase (MAPK) signalling cascade has proven to be an effective treatment for a variety of different cancers. Using an important member of this cascade, namely MEK (mitogen activated extracellular signal regulation kinase) inhibitors, the clinical responses are often transient and complete remission is rarely observed. Outgrowth of resistant clones within progressed tumours appears to be inevitable. Recent immunological and clinical observations suggest that in background of this resistance the tumour-.induced disturbance of immunoregulation at least in part may play a role. Namely, it was shown that growth factor receptor signalling pathway inhibitors can increase the immune sensitivity of tumour cells, but they can't activate the down regulated immune effectors. Consequently, the combination of MAPK cascade signalling pathway inhibitors and the immune effectors activating immunomodulators may be a promising new strategy.
Material and methods: In a now 59 years old patient with inoperable (BRAF-mutant) low differentiated adenocarcinoma of biliary ducts after 30GY radiotherapy and two cycles (Gemcitabin+ Cisplatin) chemotherapy a rapid progression of lung, liver and brain metastases were by CT and MR established. Thereafter, a treatment with BRAF+MEK inhibitors (2x150 mg dabrafenib and 1 x 2 mg trametinib) was started. These inhibitors were combined with daily 45 mg/kg rice bran arabinoxylan concentrate (using Biobran/MGN-3) which was shown to be a pathogenic associated molecular pattern (PAMP)-like molecule and can stimulate the type-1 innate immune cells against tumour cells. Results: After the chemotherapy and prior to the start of second line treatment, the patient had a nearly terminal state of her rapidly progressive disease. Eight months after the combination of MEK / BRAF inhibitor and immunomodulator therapy nearly complete remissions of all metastases was established in CT and MR.
Conclusion: This case report may support a hypothesis that MEK / BRAF inhibitors and type-1 immune cells activating immunomodulators together may synergistic inhibit the tumour growth. Further clinical investigations are necessary to clarify this question.

2017 Biobran/MGN-3, an arabinoxylan rice bran, enhances NK cell activity in geriatric subjects: A randomized, double-blind, placebo-controlled clinical trial *Ahmed F. Elsaid, Magda Shaheen and Mamdooh Ghoneum*

Aging is associated with a decline in natural killer (NK) and natural killer T (NKT) cell function that may contribute to increased susceptibility to malignancy and infection. A preliminary investigation was conducted examining the hypothesis that arabinoxylan rice bran (Biobran/MGN-3), a denatured hemicellulose with known immunomodulatory activity, could counteract this decline in NK/NKT cell activity in geriatrics. A total of 12 healthy geriatric subjects of both sexes and over 56 years old, participated in a randomized, double-blind, placebo-controlled clinical trial. A total of six subjects served as control and six subjects ingested Biobran/MGN-3 (500 mg/day) for 30 days. The effect of Biobran/MGN-3 supplementation on NK/NKT cell activity was assessed using the degranulation assay. All study subjects were monitored for the development of any inadvertent side effects. In addition, the pharmacological effects of Biobran/MGN-3 on blood cell components and liver and kidney functions were also assessed. Results demonstrated that Biobran/MGN-3 had no effect on the total percentage of NK cells, however it enhanced the cytotoxic activity of induced NK cell expression of cluster of differentiation 107a, when compared with baseline values and with the placebo group ($P<0.05$). Furthermore, there were no side effects observed, indicating that Biobran/MGN-3 supplementation was safe at the utilized dosage and for the duration of administration. Various additional beneficial effects were observed, including improved mean corpuscular volume and reduced hepatic aspartate aminotransferase enzyme levels, which suggested improved liver function. It was concluded that Biobran/MGN-3 induces a significant increase in NK activity which may increase resistance to viral infections and cancers in the geriatric population. However, additional clinical trials should be conducted in the future to verify these findings.

2017 Evidence-Based Review of BioBran/ MGN-3 Arabinoxylan Compound as a Complementary Therapy for Conventional Cancer Treatment *Soo Liang Ooi, MMath, BHSc (Comp Med) , Debbie McMullen, BHSc (Comp Med), Terry Golombick, PhD, Dipl Nut , and Sok Cheon Pak, PhD*

Introduction: Conventional cancer treatment, including surgery, chemotherapy, and radiotherapy, may not be sufficient to eradicate all malignant cells and prevent recurrence. Intensive treatment often leads to a depressed immune system, drug resistance, and toxicity, hampering the treatment outcomes. BioBran/MGN-3 Arabinoxylan is a standardized arabinoxylan concentrate which has been proposed as a plant-based immunomodulator that can restore the tumour-induced disturbance of the natural immune system, including natural killer cell activity to fight cancer, complementing conventional therapies.

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Objectives: To comprehensively review the available evidence on the effects and efficacies of MGN-3 as a complementary therapy for conventional cancer treatment.
Methods: Systematic search of journal databases and gravy literature for primary studies reporting the effects of MGN-3 on cancer and cancer treatment.
Results: Thirty full-text articles and 2 conference abstracts were included in this review. MGN-3 has been shown to possess immunomodulating anticancer effects and can work synergistically with chemotherapeutic agents, in vitro. In murine models, MGN-3 has been shown to act against carcinogenic agents, and inhibit tumour growth, either by itself or in combination with other anticancer compounds. Fourteen successful MGN-3 treated clinical cases were found. Eleven clinical studies, including 5 nonrandomized, pre-post intervention studies and 6 randomized controlled trials (RCTs) were located. Reported effects include enhanced immunoprofile, reduced side effects, improved treatment outcomes; one RCT established significantly increased survival rates. There are no reports on adverse events on MGN-3. Most of the clinical trials are small studies with short duration.
Conclusion: There is sufficient evidence suggesting MGN-3 to be an effective immunomodulator that can complement conventional cancer treatment. However, more well-designed RCTs on MGN-3 are needed to strengthen the evidence base.

2016 Controlled pilot study for cancer patients suffering from chronic fatigue syndrome due to chemotherapy treated with BioBran (MGN-3- Arabinoxylane) and targeted radiofrequency heat therapy PEER REVIEWED
*Gabriel Petrovics, Gyula Szigeti, Szilárd Hamvas, Ágnes Máté, József Betlehem, Gabriella Hegyi**
Introduction: Although modern therapies for cancer have improved life expectancy, the management of disease and improvement of quality of life (QoL) of patients, especially managing cancer-related pain and chronic fatigue syndrome are still limited. We demonstrate the efficacy of a combined therapy to treat cancer patients suffering from CFS. The effects of a combined therapy in cancer patients suffering from CFS were evaluated. NK cells were stimulated, additional tumour treatment together with targeted radiofrequency therapy (Oncothermia).
Methods: SIXTY patients with CFS (due to suffering from any type of cancer) were recruited, (according to the Centres for Disease Control 1994 criteria) attending an outpatient specialist CFS service for controlled pilot study. A total of 25 participants were given oral BioBran (MGN-3-Arabinoxylane), + Oncothermia, for six months, equivalent control group has not received this complex (BioBran + Oncothermia) treatment, they received chemo-, radiotherapy treatment.
Results: The whole body pH status showed strong tissue acidity before the treatment, but the BioBran group changed the tissue pH status. The most important finding was that the average of CFQ score was significantly reduced after the treatment, and in control group the CFQ scores did not change significantly.
Conclusion: The findings support a specific therapeutic effect of the complex BioBran+ Oncothermia therapy in CFS of cancer patients improving their QoL, enhancing NK activity in synergy.

2016 Modified rice bran hemicellulose inhibits vascular endothelial growth factor-induced angiogenesis in vitro via VEGFR2 and its downstream signalling pathways *Xia ZHU, Aya OKUBO, Naoki IGARI, Kentaro NINOMIYA and Yukari EGASHIRA*
Angiogenesis is implicated in diverse pathological conditions such as cancer, rheumatoid arthritis, psoriasis, atherosclerosis, and retinal neovascularization. In the present study, we investigated the effects of modified rice bran hemicellulose (MRBH), a water-soluble hemicellulose preparation from rice bran treated with shiitake enzymes, on vascular endothelial growth factor (VEGF)-induced angiogenesis in vitro and its mechanism. We found that MRBH significantly inhibited VEGF-induced tube formation in human umbilical vein endothelial cells (HUVECs) co-cultured with human dermal fibroblasts. We also observed that MRBH dose-dependently suppressed the VEGF-induced proliferation and migration of HUVECs. Furthermore, examination of the anti-angiogenic mechanism indicated that MRBH reduced not only VEGF-induced activation of VEGF receptor 2 but also of the downstream signalling proteins Act, extracellular signal-regulated protein kinase 1/2, and p38 mitogen-activated protein kinase. These findings suggest that MRBH has in vitro anti-angiogenic effects that are partially mediated through the inhibition of VEGF signalling.

2016 Arabinoxylan rice bran (Biobran) suppresses the viremia level in patients with chronic HCV infection: A randomized trial *Hosny Salama, Eman Medhat, Magda Shaheen, Abdel-Rahman N Zekri, Tarneem Darwish and Mamdooh Ghoneum*
Current treatments for Hepatitis C virus (HCV) have severe side effects and are very expensive. There is a need to explore effective natural therapies against HCV that are less toxic and more cost-effective. In the current study, 37 chronic HCV patients were randomized into two groups and treated with either pegylated interferon (PEG IFN) plus ribavirin (n = 21) or Biobran, an arabinoxylan from rice bran (1 g/day) (n = 16). We examined viremia, liver enzymes, interferon-γ (IFN-γ) levels in serum, and toxicity before and three months after treatment. Both groups showed a significant and similar reduction in viral load after three months of treatment relative to the baseline viral load ($P < 0.05$). In addition, treatment with Biobran resulted in a significant increase in the level of IFN-γ ($P < 0.001$). Patients in the PEG IFN plus ribavirin group showed fever, anaemia, thrombocytopenia, and easy fatigue. Patients in the Biobran group showed no side effects and reported good health. We conclude that Biobran is a potential novel therapeutic regimen that has a similar effect to PEG IFN plus ribavirin and is safe and cost-effective in the treatment of chronic HCV. Our finding of Biobran's efficacy against HCV infection warrants further investigation in multiple clinical trials (Clinical Trials Registration: NCT02690103).

2016 From Bench to Bedside: The Growing use of Arabinoxylan Rice Bran (MGN-3 /Biobran) in Cancer Immunotherapy
Mamdooh Ghoneum, Dept of Otolaryngology, Charles Drew University of Medicine and Science, USA
MGN-3/Biobran is a denatured hemicellulose obtained by reacting rice bran hemicellulose with multiple carbohydrate hydrolysing enzymes from Shiitake mushrooms. Over the last 24 years, our fundamental research objective has been to study the biotherpeutic activity of MGN-3 as a treatment for cancer based on its ability to activate the immune system. This objective has been pursued in vitro, and in animal and human studies. This review is focused on the immunomodulatory effects of MGN-3 and on its potential as an anticancer agent. In vitro studies showed that culturing different human and murine cancer cell lines with MGN-3 resulted in a

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reduction of the survival rate of cancer cells. In vivo studies have also shown that MGN-3 induces tumour regression in several models of animal bearing tumour, including gastric cancer, neuroblastoma, and Ehrlich carcinoma. In addition, the anti-cancer activity of MGN-3 has been shown in human clinical trials and in several case reports on patients with Hepatocellular Carcinoma (HCC) and progressive and partially metastasized cancer. Patients that were treated with MGN-3 in addition to Conventional Therapy (CT), as compared with CT alone, showed: 1) less recurrence of cancer, 2) higher survival rate and 3) improved Quality of Life (QOL) as characterized by improvements in physical activity, appetite, sleep, and digestion, and a decrease in pain and anxiety. This review summarizes the preclinical and clinical research on MGN-3/Biobran since it was first patented in 1992. Various animal studies and human clinical trials including different types of malignancies have demonstrated that MGN-3 is a potent Biological Response Modifer (BRM). MGN-3 enhances the cytotoxic reactivity of immune cells with anti-cancer activity such as NK and CD8+ T cells via increasing cell granularity, stimulates the production of interferons, IL-2 and IL-12, and functions as a natural adjuvant for Dendritic Cells (DC). Therefore, MGN-3 may be used in DC-based vaccine strategies against infections and cancer. Importantly, MGN-3 is a unique BRM because it is a safe non-toxic agent and does not exhibit hyporesponsiveness. MGN-3 has the potential to be a novel and promising immune modulatory adjuvant that could complement the existing immunotherapeutic modalities for cancer patients.

2015 Home Products Research Distributors Contact Can a synergistic activation of pattern recognition receptors by plant immunomodulators enhances the effect of oncologic therapy? Case Report of a patient with uterus and ovary sarcoma

Tibor Hajto, Lilla Baranyai, Angelika Kirsch, Monika Kuzma and Pal Perjési

Background: Growing evidence supports the hypothesis that similar to microbes various plant extracts can also contain Pathogenic Associated Molecular Pattern (PAMP)-like structures which can activate type-1 cellular functions of the innate immune system. Since they are important in tumour defence and the chemical production of PAMP structures is hardly accomplishable, the plant extracts standardized concerning their PAMP like structures may be promising for future tumour therapy.

Method: The synergistic effect of two standardized plant immunomodulators was monitored by the hemocytological measurement of the peripheral level of Natural Killer (NK) cells. Suboptimal doses of istletoe lectins (ML) and Arabinoxylan in MGN-3 were compared using healthy volunteers.

Results: 24h after a single suboptimal dose (15 mg/kg) of Arabinoxylan in MGN-3 an average increase (+/-SEM) in NK level was 46.4 (+/-36)% and 24h after a single suboptimal (0.45 ng/kg) ML injection a 36 (+/-13) % enhancement was found. If these suboptimal doses of Arabinoxylan and ML were given together, a highly significant enhancement (293 +/-41%) was established indicating a high significant synergism between them ($p<0.001$). A patient with uterus and ovary sarcoma was not able to tolerate the CYVADIC chemotherapy. After its combination with ML and Arabinoxylan using optimal doses: 0.75 ng/kg and 45 mg/kg respectively, she received six cycles CYVADIC and thereafter only immunotherapy was given. During the following five years she has regularly been tumour free.

Conclusion: The combination of standardized plant extracts with PAMP-like structures seems to open new perspectives in the supportive therapy of metastatic tumours. Further research is necessary.

2015 Arabinoxylan rice bran (MGN-3/Biobran) enhances natural killer cell — mediated cytotoxicity against neuroblastoma in vitro and in vivo PEER REVIEWED

Anton Pérez-Martínez, Jaime Valentín, Lucía Fernández, Enrique Hernández-Jiménez, Eduardo López—Collazo, Petra Zerbes, Ellen Schworer, Fernando Nuñéz, Inmaculada Génesis Martín, Hannah Sallis, Miguel Ángel Díaz, Rupert Handgretinger & Matthias Manuel Pfeiffer

Background aims: Natural killer cell (NK) cytotoxic activity plays a major role in natural immunologic defences against malignancies. NK cells are emerging as a tool for adoptive cancer immunotherapies. Arabinoxylan rice bran (MGN-3/Biobran) has been described as a biological response modifier that can enhance the cytotoxic activity of NK cells. This study evaluated the effect of MGN-3/Biobran on NK cell activation, expansion and cytotoxicity against neuroblastoma cells. Methods: NK cells were enriched with magnetic beads and stimulated with MGN-3/Biobran. NK cell activation was evaluated via analysis of their phenotype, and their expansion capability was tracked. The in vitro cytotoxic ability of the activated NK cells was tested against K562, Jurkat, A673, NB1691, A-204, RD and RH-30 cell lines and the in vivo cytotoxic ability against the NB1691 cell line. Results: MGN-3/Biobran stimulation of NK cells induced a higher expression of the activation associated receptors CD25 and CD69 than in unstimulated cells ($P < 0.05$). The expression of NKG2D, DNAM, NCRs and TLRs remained unchanged. Overnight MGN-3/Biobran stimulation increased NK cell cytotoxic activity against all cell lines tested in vitro and decelerated neuroblastoma growth in vivo. The mechanism is not mediated by lipopolysaccharide contamination in MGN-3/Biobran. Furthermore, the addition of MGN-3/Biobran promoted NK cell expansion and decreased T cells in vitro. Conclusions: Our data show that MGN-3/Biobran upregulates NK cell activation markers stimulates NK cell cytotoxic activity against neuroblastoma in vitro and in vivo and selectively augments the expansion of NK cells. These results may be useful for future NK cell therapeutic strategies of the treatment of neuroblastoma.

2014 Modified Arabinoxylan from Rice Bran, MGN-3/Biobran, Sensitizes Metastatic Breast Cancer Cells to Paclitaxel In Vitro

Mamdooh Ghoneum, Nariman K. Badr El-Din, Doaa A. Ali and Mai Alaa El-Dein

There is an increased interest in alternative treatments that reduce the toxicity of chemotherapy by lowering the drug concentration, whilst maintaining potency against cancer cells. Previous studies have demonstrated that arabinoxylan from rice bran, MGN-3/Biobran, sensitizes human breast cancer cells (BCC) to daunorubicin (DNR). In the present study, we further evaluated the ability of MGN-3 to sensitize cells to another chemotherapy agent, paclitaxel. Materials and Methods: Non-metastatic MCF-7 (human BCC) and metastatic 4T1 (murine BCC) cells were cultured with different concentrations of paclitaxel in the presence or absence of MGN-3. Cell survival, DNA damage, and cell proliferation were examined. Results: MGN-3 increased the susceptibility of both types of cancer cells to paclitaxel by over 100-fold. Mechanistically, MGN-3 works synergistically with paclitaxel by causing DNA damage, enhancing apoptosis, and inhibiting cell proliferation in 4T1 cells. Conclusion: Our data demonstrate that MGN-3 is an effective chemosensitizer and may represent a novel adjuvant for the treatment of metastatic breast cancer.

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2014 Therapeutic Effects of Biobran, Modified Arabinoxylan Rice Bran, in Improving Symptoms of Diarrhea Predominant or Mixed Type Irritable Bowel Syndrome: A Pilot, Randomized Controlled Study PEER REVIEWED

Takeshi Kamiya, Michiko Shikano, Mamoru Tanaka, Keiji Ozeki, Masahide Ebi, Takahito Katano, Shingo Hamano, Hirotaka Nishiwaki, Hironobu Tsukamoto, Tsutomu Mizoshita, Yoshinori Mori, Eiji Kubota, Satoshi Tanida, Hiromi Kataoka, Noriaki Okuda, and Takashi Joh

Recently, it was revealed that low grade mucosal inflammation and/or immune imbalance of the lower digestive tract is one of the mechanisms involved in symptom generation in patients with irritable bowel syndrome (IBS). Biobran, arabinoxylan compound derived from rice bran, has been reported to have several biological actions such as anti-inflammatory and immune modulatory effects. So we investigated the therapeutic effects of Biobran in patients with IBS. Method: Forty patients with diarrhoea predominant or mixed type IBS were randomly assigned to either a Biobran group for treatment with Biobran or a placebo group. Therapeutic efficacy and IBS symptoms were assessed subjectively by the patients after 4 weeks of administration. Results: The global assessment was effective in 63.2% of the Biobran group and in 30% of the placebo group ($P < 0.05$, Biobran group versus placebo group). Biobran group showed a significant decrease in the score of diarrhoea and constipation and in CRP value. However, no significant changes were observed in the placebo group. Conclusion: The administration of Biobran improved IBS symptoms. It is likely that anti-inflammatory and/or immune modulatory effects of Biobran might be useful in IBS patients.

2014 MGN-3/BIOBRAN Enhances Generation of Cytotoxic CD8+ T Cells Via Upregulation of DEC-205 Expression on Dendritic Cells *M. Ghoneum and S. Agrawal* PEER REVIEWED

Arabinoxylan rice bran (MGN-3/Biobran) has been shown to be a potent biological response modifier (BRM) that activates different arms of the immune system, including dendritic cells (DCs), which prime CD4+ helper T-cell responses. The present study explores the ability of MGN-3-activated DCs to prime CD8+ T cells and examines the mechanisms underlying its effect. Human monocyte-derived DCs were treated with MGN-3 (20 and 40 µg/ml). Results indicate that treatment with MGN-3 caused DCs to prime higher granzyme B-expressing CD8+ T cells. Tumour lysate-pulsed MGN-3 DC also increased tumour cell killing compared to DC-stimulated CD8+ T cells. This was associated with: i) increased expression of DEC-205 in MGN-3-activated DCs in a dose—dependent manner; and ii) MGN-3 induced significant production of Type III interferon, IL29, but not Type I IFNs on and B. These results suggest that MGN-3 is a potent natural adjuvant that efficiently activates DCs and may therefore be useful for mounting an efficient immune response against infections and cancer.

2013 Biobran MGN-3: Effect of reducing side effects of chemotherapy in breast cancer patients *Masood AI, Sheikh R, Anwer RA*

Objective: The aim of study was to assess the effect of Biobran in reducing of chemotherapy induced side effects in terms of tiredness, anorexia, vomiting and hair loss and quality of life in terms of weight loss.

Setting: Radiotherapy Department, Nishtar Hospital Multan.

Material and Methods: Fifty patients of breast cancer were enrolled randomly in two groups. Group—A patients were given 3 gram dose of Biobran MGN-3 per day one week before and one week after chemotherapy. Group-B patient were given chemotherapy alone. Total six cycles of chemotherapy were given. No multivitamin or food supplements were given during this study. Chemotherapy induced side effects (tiredness, anorexia, and vomiting, hair loss) were assessed by questionnaire to the patients before start of each cycle. Weight was checked before each cycle to assess weight gain or loss. White blood cells were checked by complete blood count just before and one week after chemotherapy.

Results: Between six months, 50 patients were enrolled in Radiotherapy Department, Nishtar Hospital Multan. There was a significant reduction in tiredness and anorexia in group—A patients. 20 (80%) patients of group-A felt increase in their diet and no tiredness without any appetizer or multivitamin. But group—B patients demanded for appetizer due to severe anorexia after chemotherapy except 3 (12%) patients who didn't use any appetizer or food supplement. In group-A, 15 (60%) patients didn't need any anti-emetic as compared to group-B all patient (100%) experienced severe nausea during and after chemotherapy. Group—A patients experienced less hair fall 7 (28%) patients as compared to other group which is 25 (100%) patients.

Conclusions: The study showed that, by helping to optimize the immune system, Biobran MGN-3 can not only help maximize treatment success, but also minimize treatment side effects and improve quality of life during treatment and in recovery.

2013 Case Reports of Cancer Patients with Hepatic Metastases Treated by Standardized Plant Immunomodulatory Preparations *Tibor Hajto and Angelika Kirsch* PEER REVIEWED

Background: Metastatic hepatocellular carcinoma often has a multifocal tumour pattern with markedly depressed hepatic function, Hepatic resection in many cases results in no long-term benefit. After a chemotherapy hepatic tumours rarely disappear completely and the duration of responses is short, In the last decades growing evidence suggested that a disturbed balance in the innate system can also play a role in the poor prognosis of hepatic tumours.

Objectives: The aim of this article is to present and discuss several favourable clinical responses of patients with hepatic metastases who parallel to conventional oncologic therapy, were treated with immunologically effective and standardized plant extracts.

Course of Therapy and Results: In accordance with the bell-shaped dose-response relationship of mistletoe lectins (MLs), the patients were treated with a fermented mistletoe extract (ME) preparation, standardized for the active sugar-binding lectin contents, Thus, an optimal dose between 0.5 and 1,0ng/kg MLs was given twice a week subcutaneously. In addition to ML therapy, a heteropolysaccharide rice bran preparation standardized for arabinoxylan (12-45mg/kg MGN-3/Biobran twice a week) and wheat germ extract (WGE) standardized for 2, 6-dimethoxy-p-benzoquinone (50-80mg/kg AvemarR four times a week) was also given. In these case reports the clinical progress of seven patients showed a complete or nearly complete remission of hepatic metastases.

Conclusion: ML, MGN-3 and WGE seem to be potent candidates to be regarded as a supportive therapy to surgery, hormone treatment or chemotherapy for patients with hepatic metastases. These case reports require further clinical studies.

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2012 Suppressive Effect of Modified Arabinoxylan from Rice Bran (MGN-3) on D-Galactosamine-Induced IL-18 Expression and Hepatitis in Rats *S. Zheng, H. Sanada, H. Dohi, S. Hirai and Y. Egashira* PEER REVIEWED

We investigated in this study the effect of modified arabinoxylan from rice bran (MGN-3) and its fractions on D-galactosamine (D-GalN)-induced IL-18 expression and hepatitis in rats. Male Wistar rats were pre-treated with MGN-3 or fractions of the MGN-3 hydrolysate, or with saline 1 h before administering D-GalN (400 mg/kg B.W.). The serum transaminase activities, IL-18 mRNA expression level in the liver and IL-18 concentration in the serum were determined 24h after injecting D-GalN. Both the oral and intraperitoneal administration of MGN-3 (20 mg/kg B.W.) alleviated D-GalN-induced hepatic injury under these experimental conditions. The low-molecular-weight fraction (LMW) of MGN-3 showed the strongest protective effect on D-GalN-induced liver injury, its main sugar component being glucose. Moreover, the D-GalN-induced IL-18 expression was significantly reduced by treating with MGN-3 and LMW. The results suggest that MGN-3 and LMW could provide significant protection against D-GalN liver injury, and that IL-18 might be involved in their protective influence.

2012 Chemopreventive Properties of Dietary Rice Bran: Current Status and Future Prospects PEER REVIEWED

Angela J. Henderson, Cadie A. Ollila, Ajay Kumar, Erica C. Borresen, Komal Raina, Rajesh Agarwal and Elizabeth P. Ryan.

Emerging evidence suggests that dietary rice bran may exert beneficial effects against several types of cancer, such as breast, lung, liver, and colorectal cancer. The chemopreventive potential has been related to the bioactive phytochemrcals present in the bran portion of the rice such as ferulic acid, tricin,B-sitosterol, y-oryzanol, tocotrienols/tocopherols, and phytic acid.

Studies have shown that the anticancer effects of the rice bran-derived bioactive components are mediated through their ability to induce apoptosis, inhibit cell proliferation, and alter cell cycle progression in malignant cells. Rice bran bioactive components protect against tissue damage through the scavenging of free radicals and the blocking of chronic inflammatory responses.

Rice bran phytochemicals have also been show to activate anticancer immune responses as well as affecting the colonic tumour microenvironment in favour of enhanced colorectal cancer chemoprevention. This is accomplished through the modulation of gut microflora communities and the regulation of carcinogen metabolizing enzymes. In addition, the low cost of rice production and the accessibility of rice bran make it an appealing candidate for global dietary chemoprevention. Therefore, the establishment of dietary rice bran as a practical food-derived chemopreventive agent has the potential to have a significant impact on cancer prevention for the global population.

2012 An Open-label, randomized clinical trial to assess the immunomodulatory activity of a novel oligosaccharide compound in healthy adult PEER REVIEWED

K. H. Ali, A. B. Melillo, S. M. Leonard, D. Asthana, Judi M. Woolger, A. H. Wolfson, H. R. McDaniel, J. E. Lewis

Rice Bran Arabinoxylan Compound (RBAC) is a nutritional supplement produced by enzymatic hydrolysis of hemicellulose B derived from rice bran. Several in vitro studies and clinical reports have shown RBAC to possess promising immunomodulating effects, specifically with respect to natural killer cell and cytokine activity. The concept of a true immunomodulator is an agent possessing a broad range of activity dependent upon the existing state of health and immunity in the individual host. The present study investigated the immunomodulatory effect of RBAC in a healthy adult human population over 60 days by assessing changes in natural killer cell cytotoxicity (NKCC) and cytokines and growth factors. Subjects participated in a two-group, randomized intervention, where one group (n=10) consumed 1 gram/day and the other (n=10) consumed 3 gram/day. Safety and tolerability of RBAC were assessed with total bilirubin, total protein, creatinine, and liver function tests.

2012 MGN-3 arabinoxylan rice bran modulates innate immunity in multiple myeloma patients PEER REVIEWED

Danna Cholujova, Jana Jakubikova, Brarnislav Czako, Michaela Marisova, Luba Hunakova, Jozef Duraj, Martin Mistrik, Jan Sedlak.

Dendritic cells (DCs) and natural killer (NK) cells are central components of innate immunity for controlling tumour growth. The therapeutic effects of certain anti-myeloma drugs are partially mediated by targeting the innate immune response. In addition, novel types of natural compounds have been developed that efficiently modulate the activity of both the cellular and humoral compartments of immunity. MGN-3 is known as an activator of natural killer cells, inducer of apoptosis and cytokine production, and modulator of dendritic cell maturation and differentiation in vitro. We have performed a randomized, placebo-controlled study to examine the effects of MGN-3 on innate immune system parameters in 48 multiple myeloma patients. We performed immunophenotypic analysis of peripheral blood samples, determined NK cell activity, and assessed the cytokine profiles of plasma before and during 3 months of treatment. The results demonstrate a clear increase in NK activity in MGN-3-treated patients compared to the placebo group, an increased level of myeloid DCs in peripheral blood, and augmented concentrations of T helper cell type 1-related cytokines. The present study suggests that MGN-3 may represent an immunologically relevant product for activating innate immunity in multiple myeloma patients and warrants further testing to demonstrate clinical efficacy. Protective effect of low molecular fraction of MGN-3, a modified arabinoxylan from rice bran, on acute liver injury by inhibition of

2012 Protective effect of low molecular fraction of MGN-3, a modified arabinoxylan from rice bran, on acute liver injury by inhibition of NF-kB and JNK/MAPK expression *Surina Zheng, Shunsuke Sugita, Shizuka Hirai, Yukari Egashira* PEER REVIEWED

D-Galactosamine (GaIN) induces acute hepatitis in experimental animals; this hepatitis has been shown to be suppressed by oral or intraperitoneal administration of modified arabinoxylan from rice bran (MGN—3), and active low molecular fraction isolated from MGN-3 (LMW). We previously reported that this protective mechanism is mediated in part by downregulation of interleukin-18 (IL-18), The present study shows for the Hrst time that nuclear factor- κB (NF- κB), mitogen-activated protein kinase (MAPK) and CD14 are involved in the suppressive action of LMW on GaIN-induced hepatitis Wistar rats (aged 4 weeks, SLC) were intraperitoneally treated with either MGN—3 or LMW. Then, rats were given GaIN at 400 mg/kg at 1 h after the initial treatment, the serum activity of transaminases (ALT and AST) was significantly higher after GaIN treatment: these changes were attenuated by MGN—3 and LMW. Furthermore, LMW abrogated inhibitor of κB kinase (I κB) degradation induced by GaIN, and this was associated with the inhibition of NF κB activation. Moreover, phosphorylated stress-activated protein kinase/c-jun N-terminal kinase (JNK)

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protein expression in the liver after GaIN treatment was significantly higher, and LMW reduced this increase. We also found that GaIN treatment induced TLR4 and CD14 mRNA expression, and LMW significantly inhibited CD14 mRNA expression. These results suggest that the suppressive effects of LMW on GaIN—induced hepatitis are possibly related to inhibition of NF- κB,NK phosphorylation and CD14 expression.

2012 Arabinoxylan rice bran (MGN-3/Biobran) provides protection against whole-body γ-irradiation in mice via restoration of hematopoietic tissues PEER REVIEWED

Mamdooh Ghoneum, Nariman K. Badr El-Din, Salma M. Abdel Fattah and Lucilene Tolentino

The aim of the current study is to examine the protective effect of MGN-3 on overall maintenance of hematopoietic tissue after γ-irradiation. MGN-3 is an arabinoxylan from rice bran that has been shown to be a powerful antioxidant and immune modulator. Swiss albino mice were treated with MGN-3 prior to irradiation and continued to receive MGN-3 for 1 or 4 weeks, Results were compared with mice that received radiation (5 Gy rays) only, MGN-3 (40 mg/kg) only and control mice (receiving neither radiation nor MGN-3). At 1 and 4 weeks post-irradiation, different hematological, histopathological and biochemical parameters were examined. Mice exposed to irradiation alone showed significant depression in their complete blood count (CBC) except for neutrophilia. Additionally, histopathological studies showed hypocellularity of their bone marrow, as well as a remarkable decrease in splenic weight/relative size and in number of megakaryocytes. In contrast, pre-treatment with MGN-3 resulted in protection against irradiation-induced damage to the CBC parameters associated with complete bone marrow cellularity, as well as protection of the aforementioned splenic changes. Furthermore, MGN-3 exerted antioxidative activity in whole-body irradiated mice, and provided protection from irradiation-induced loss of body and organ weight. In conclusion, MGN-3 has the potential to protect progenitor cells in the bone marrow, which suggests the possible use of MGN-3/Biobran as an adjuvant treatment to counteract the severe adverse side effects associated with radiation therapy.

2011 Activation of Human Monocyte-Derived Dendritic Cells In Vitro by the Biological Response Modifier Arabinoxylan Rice Bran (MGN-3/Biobran) *M. Ghoneum and S. Agrawal* PEER REVIEWED

Arabinoxylan rice bran (MGN—3/Biobran) is a potent biological response modifier (BRM) that activates natural killer (NK) cells, T cells and monocytes. Currently, little is known regarding the effects of MGN-3 on dendritic cells (DCs), the cell type that bridges innate and adaptive immunity. Therefore, we examined the stimulatory effects of MGN-3 on DCs. Human monocyte-derived DCs were treated with MGN-3 at different concentrations (5-20 μg/ml) for 24 hours in vitro. Activation of DCs was determined by assessing the expression of co-stimulatory and maturation markers (CD40, CD80, CD83, CD86 and HLA-DR) by flow cytometry, and production of cytokines by ELISA. DC function was determined by assessing their ability to activate naive T cells. Activation of T cells was assessed by measuring cell proliferation and cytokine production. MGN-3 treatment, in a dose-dependent manner, resulted in: 1) up-regulation of the surface expression of CD83 and CD86, on DCs; 2) an increase in the production ofpro-inflammatory and immuno—regulatory cytokines (IL-lβ}, IL-6, IL-10, TNF-α, IL-12p40 and low levels of IL-12p70 and IL-2) by DCs; and 3) MGN-3 stimulated DC induced CD4T cell proliferation and their production of cytokines, IFN-7, lL-10, IL-17. Results suggest that MGN-3 functions as a natural adjuvant for DC activation and thus may be used in DC-based vaccine strategies against infections and cancer.

2011 The clinical effectiveness of BioBran in immunotherapy for patients with hepatitis B *Dr. Tran Thi Minh Phuong*

Hepatitis B virus (HBV) infection is a serious global health problem with devastating consequences of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. More efficacious treatments, mass immunization programs, and safe injection techniques are essential for eliminating HBV infection and reducing global HBV-related morbidity and mortality. Antiviral therapy has been the primary treatments to date. However, conventional treatment has undesirable side-effects and continuous treatment can lead to the development of resistance. In addition, antiviral medicines are costly, thousands of dollars per year, and are not widely available in many countries, especially in the developing world. BioBran is a food supplement that is combined with conventional treatment to improve the outcome of the disease. There were 3 cases of viral B hepatitis patients who have treated by the combination of conventional antiviral therapy and BioBran were described. In these cases, blood samples were taken to measure liver function and immunopotency, and the results were compared with changes in clinical and image condition. Improvements were noted in most of the cases. Finally, some remarks were provided to enhance the effectiveness of treatment progress.

2011 Synergistic apoptotic effect of Arabinoxylan rice bran (MGN-3/Biobran) and Curcumin (Turmeric) on human multiple myeloma cell line U266 in vitro *M. Ghoneum, S. Gollapudi* PEER REVIEWED

The present study was carried out to investigate the synergistic apoptotic potential of arabinoxylan rice bran (MGN-3/Biobran) and curcumin (turmeric) on human multiple myeloma (MM) cell line U266 , in vitro. U266 cells were cultured with MGN-3 (50 or 100μg/ml) and curcumin (2.5-10μM) for 3 days. The effects of MGN-3 and curcumin on the growth and survival of the U266 cells were determined by trypan blue, MTT assay flow cytometry analysis of cancer cell cycle, and apoptosis. Expression of proapoptotic Bax, and antiapoptotic Bcl2 was determined by Western blot analysis. Treatment with MGN—3 alone or curcumin alone caused a dose-dependent inhibition in the proliferation ofU266 cells. However, a synergistic effect was noticed post-treatment with both agents that maximized at 100μg/ml MGN-3 plus 10μM curcumin. This synergy was characterized by an 87% decrease in cell number and a 2.6 fold increase in the percentage of apoptotic U266 cells, Cell cycle analysis showed a 53% decrease in the percentage of cells in the G0-G1 phase treated with MGN-3 and curcumin (from 36% to 17%). Analysis of the expression of the pro and antiapoptotic molecules Bax and Bcl-2 revealed synergistic effects of these agents, as the expression of Bcl-2 was decreased and Bax was increased. This resulted in a cellular microenvironment favourable for apoptosis. We conclude that MGN-3 and curcumin synergize in the induction of U266 cell apoptosis. This data may establish the foundation for in viva studies that could have therapeutic implications.

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2010 Arabinoxylan Rice Bran (MGN-3) enhances the Effects of Interventional Therapies for the Treatment of Hepatocellular Carcinoma: A Three-year Randomized Clinical Trial PEER REVIEWED

Mai Hong Bang, Tran Van Piep, Nguyen Tien Thinh, Le Huu Song, Trinh Tuan Dung, Le Van Truong, Le Van Don, Thai Doan Ky, Deyu Pan, Magda Shaheen and Mamdooh Ghoneumm

Background and Aims: This study examined the efficacy of arabinoxylan rice bran (MGN-3) in conjunction with an interventional therapy (IT) for the treatment of hepatocellular carcinoma patients. Patients and Methods: A total of sixty-eight patients with hepatocellular carcinoma (stages I and II) participated in the study. Patients were randomized to receive IT (30 patients, control group) or IT+MGN-3 (38 patients), and randomly divided into two groups using a computer-generated randomization list. Patients and investigators were blinded. IT included trans arterial oily chernoembolization (TOCE) or a combination of TOCE and percutaneous ethanol injection treatment (PEIT). Results: Patients in the IT+MGN-3 group showed: (i) lower recurrence of the disease, 3l.6% (I2/38), as compared to 46.7% (I4/30) for the control; (ii) higher survival aher the second year, 35%, as compared to 6.7% for the control; (iii) significantly lower alpha-fetoprotein level, a 38% decrease (p=0,()001), as compared to baseline value, while the control showed no significant change; and (iv) a significant decrease in tumour volume, in contrast to the control, which showed no significant change. When the results were analysed according to each IT modality, MGN-3+IT sub-groups displayed a greater response to treatment, in every aspect examined, than the IT sub-groups alone, How even the patients in the MGN-3+TOCE+PEIT sub-group demonstrated greater reduction in AFP levels and longer survival time than the MGN-3+TOCE; sub-group. Conclusion: MGN-3 in conjunction with IT may be useful at the treatment of hepatocellular carcinoma and warrants farther investigation in multiple clinical trials.

2009 Biobran-augmented maturation of human monocyte derived dendritic cells PEER REVIEWED

D.Cholujova, J.Jakubikova, J.Sedlak

BioBran, enzymatically modified arabinoxylan from rice bran was tested for its possible effects on in vitro maturation of human dendritic cells (DC). lmmature DC (iDC) derived from plastic-adhered, lL-4 and GM-CSF treated peripheral monocytes (Mo) were further cultured with cytokine maturation mix l (CMMl; TNF-alfa, lL-1[5 and 1L-6) or CMM2 (LPS and IFN-y) to induce their maturation into mature DC (matDCl or matDC2, respectively). Different concentrations of BioBran (10, 100, 400 and 1000 ug/ml) were applied in the presence or absence of relevant CMM to assess the effects of BioBran on DC maturation processes. BioBran induced maturation of iDC, as these cells cultured with IL-4/GM-CSF/BioBran down-regulated CD14 and CD1a antigens on cell surface and significantly increased expression of maturation marker CD83. The increase of surface density of costimulatory molecules CD80 and CD86 on iDC in the presence of BioBran was also observed. In addition, BioBran induced functional maturation of iDC, confirmed by decreased endocytic activity of iDC, Furthermore, BioBran enhanced maturation potential of cytokine mixes, as both matDC1 and matDC2 exposed to BioBran completely lost CD14 and upregulated CD83, CDS0 and CD86 antigens, in comparison to DC matured with the relevant CMM alone. BioBran also increased CD123 antigen expression on all DC subsets. Interestingly, matDC2 matured in the presence of BioBran (400ug/ml) expressed higher levels of CD123 and lower levels of CD11c cell surface antigens, the phenotype represented by CD11c CD123 plasmacytoid DC population. These data demonstrate that BioBran is a potent enhancer of DC maturation and suggest that BioBran might be a useful agent to create the environment that favours DC maturation.

2008 In Vivo Tumor Inhibitory Effects of Nutritional Rice Bran Supplement MGN-3/Biobran on Ehrlich Carcinoma-Bearing Mice *N. El-Din, E. Noaman and M. Ghoneum* PEER REVIEWED

This study was undertaken to investigate the in vivo anti-tumour activity of MGN-3/Biobran, a modified arabinoxylan rice bran. Swiss albino mice were inoculated intramuscularly in the right thigh with Ehrlich ascites carcinoma (EAC) cells. On Day 8, mice bearing a solid Ehrlich carcinoma (SEC) tumour were treated with MGN-3 via intraperitoneal injection. Tumour growth, cytokine pro-duction, and apoptotic effect of MGN-3 were examined. MGN-3 caused a highly significant delay in both tumour volume (63.27%) and tumor weight (45.2%) as compared to controls ($P < 0.01$). The mechanisms by which MGN-3 exerts its antitumor effect seem to involve its ability to induce apoptosis and immune modulation. MGN-3 induced a 1.8-fold increase in the percentage of apoptotic SEC cells as determined by flow cytometry and the histopathological examination. In addition, MGN-3 influenced plasma cytokine production by increasing the levels of tumour necrosis factor-az and interferon-γ, while downregulating levels of the immune suppressing cytokine interleukin-10. Data also showed that non-tumour-bearing mice intramuscularly injected with MGN-3 resulted in a twofold increase in natural killer activity. No adverse side effects due to MGN-3 treatment were observed; all animals displayed normal feeding/drinking and life activity patterns. These data may have clinical implications for the treatment of solid cancers.

2008 Modified Arabinoxylan Rice Bran (MGN-3/Biobran) Enhances Intracellular Killing of Microbes by Human Phagocytic Cells In Vitro *M. Ghoneum, M. Matsuura and S. Gollapudi* PEER REVIEWED

Phagocytic cells, comprised of neutrophils and monocytes/macrophages, play a key role in the innate immune response to infection. Our earlier study demonstrated that arabinoxylan rice bran (MGN-3/Biobran) activates murine peritoneal macrophage and macrophage cell lines. ln this study, we investigated whether MGN-3 can upregulate the phagocytic activity of human phagocytes in peripheral blood to phagocytize Escherichia coli (E. coli), trigger the oxidative burst and produce cytokines. Phagocytic cells were pre-labeled with dichlorofluorescin diacetate dye and were incubated with phycoerythrin-labeled. E. coli in the presence or absence of MGN-3. Phagocytosis and oxidative burst were assessed by flow cytometry. Results showed that treatment with MGN-3 enhanced the phagocytosis of E. coli by neutrophils and monocytes. This was associated with an increased oxidative burst. ln addition, it caused a significant induction of cytokines (TNF-α, IL-6, IL-8 and lL—10); the effect was detected at 1 µg/ml and increased in a dose—dependent manner (P5 0.01). Notably, MGN-3 alone had no effect on the growth of 31 strains of bacteria suggesting that MGN-3 modulates phagocytic cellular function. These findings may have applications in the treatment of infections in the elderly and in immunocompromised patients.

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2008 MGN-3/Biobran, modified arabinoxylan from rice bran, sensitizes human breast cancer cells to chemotherapeutic agent, daunorubicin *S. Gollapudi and M. Ghoneum* PEER REVIEWED

MGN-3/Biobran, a modified form of arabinoxylan from rice bran, is a potent biological response modifier (BRM). Our previous studies demonstrated that MGN-3 sensitizes human leukaemia cells to death receptor [CD95]-induced apoptosis [Ghoneum M, Gollapudi S. MGN-3 sensitizes human T cell leukaemia cells to death receptor (CD95)-induced apoptosis. Cancer Lett 2003; 20l :41-9]. In this study, we evaluated the chemo-sensitizing activity of MGN-3 against human breast cancer cells (BCCs) in vitro. Methods: BCCs (MCF-7 and HCC70 cells) were cultured with different concentrations of daunorubicin (DNR) (from 1 x10^{-9} to 1×10^{-6}M) in the presence or absence of selected concentrations of MGN-3 (100—1000 µg/ml) for 3 days. Cancer cell survival was determined by MTT assay and drug accumulation was determined by flow cytometry. Results: Treatment with MGN-3 increased susceptibility of BCCs to DNR (5.5 –fold for MCF-7 and 2.5-fold for HCC70 cells) as compared to BCCs treated with DNR alone. The sensitizing effect of MGN-3 was associated with increased accumulation of DNR in cancer cells. Conclusions: Our data demonstrate that MGN-3 is an effective chemo-sensitizer and may represent a potential novel adjuvant for the treatment of breast cancer.

2008 Modulation of the anticancer immunity by natural agents: inhibition of T regulatory lymphocyte generation by arabinoxylan in patients with locally limited or metastatic solid tumours *P. Lissoni, G. Messina, F. Brivio, L. Fumagalli, L. Vigore, F. Rovelli, L. Maruelli, M. Miceli, P. Marchiori, G. Porro, M. Held, G. di Fede, T Uchiyamada* PEER REVIEWED

In the last years, several immunomodulating antitumor agents have demonstrated in the nature, particularly from Aloe plant and rice bran. However, the major problem concerning the natural antitumor agents is to define their immune mechanisms of action in relation to the more recent advances in tumour immunobiology. At present, the main cause responsible for the lack of an effective antitumor response in advanced cancer patients is believed to be represented by the generation of a subtype of T helper lymphocytes (CD4) with suppressive activity on anticancer immunity, the so-called T regulatory lymphocytes (T reg), which may be clinically identified as CD4*CD25* cells. On this basis, a study was planned to evaluate the effect of rice bran extract arabinoxylan on T reg cell count and percentage in solid tumour patients in relation to the various lymphocyte subpopulations. The study included 22 evaluable cancer patients, 16 of whom had an untreatable metastatic solid tumour. Arabinoxylan was given orally at a dose of 2000 mg/day for the first month, followed by a dose of 1000 mg/day for the next month. In each patient we evaluated by monoclonal antibodies the absolute number of lymphocytes, T lymphocytes (CD3*), T helper (TH) lymphocytes (CD4*), T cytotoxic lymphocytes (CD8*), NK cells (CD16*CD56*), T reg lymphocytes (CD4*CD25*) and TH/T reg ratio before and after 2 months of therapy. No substantial change occurred on therapy in the mean number of lymphocytes, CD3*, CD8* and NK cells. On the other hand, the mean number of TH cells increased, whereas that of T reg cell decreased on treatment, even though none of these differences was statistically significant. On the contrary, TH/T reg mean ratio significantly enhanced after arabinoxylan therapy. In addition to its previously demonstrated stimulatory action on NK function, this study shows that arabinoxylan may inhibit the production of T reg cells, which are responsible for cancer-related immunosuppression, with a following improvement in the anticancer immunity. If further studies will confirm these results, arabinoxylan could be successfully associated with chemotherapy to induce not only a cytotoxic destruction of cancer cells, but also an improvement in the immune status.

2008 Epigenetics and Immunosenescence Reversal: An Evidence-Based Longevity Paradigm *Karriem H. Ali, M.D.*

Humankind has long thought of aging as a gradual, time-dependent, deterioration in one's well-being and quality of life, with an increased incidence and severity of debilitating chronic diseases. However, current medical opinion argues for a fresh, and more enlightened perspective on aging. Indeed, until recently, clinical medicine has focused more upon mitigating the effects of aging rather than reversing the process itself. However, current developments in epigenetics and immunology mean that we are now ready to begin the greater challenge of halting or reversing the aging process. There is a vast body of scientific literature indicating that immune dysregulation — specifically of the innate immune system — may be the determinative factor for the seemingly inevitable functional decline of advancing age. This dysregulation is characterized by a continual, low—grade, over-reactive state of systemic immune processes, which promote, in whole or in part, the pathognomonic signs of many of the chronic diseases that we associate with aging (e.g., cardiovascular disease, Alzheimer's disease, cancer, osteoarthritis, insulin—resistance, and diabetes).

2008	Oct.	"The Anti-inflammatory and Immunomodulating Effects of Rice Bran Arabinoxylan Compound on Irritable Bowel Syndrome", *The 50th Annual Meeting of the Japanese Society of Gastroenterology Journal of Gastroenterology, Tokyo, JAPAN,* Kamiya T., Shikano M. and T.

2007	Jun.	"Rice Bran Supplement (MGN-3/Biobran) Suppresses Tumor Growth via Modulating Cytokine Production and Increasing Apoptotic Level in Ehrlich Carcinoma-bearing Mice", *Federation of clinical immunology Society (FOCiS2007), San Diego, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science), et al.

2006	Jun.	"Effect of Modified Arabinoxylan from Rice Bran (MGN-3/BioBran) On Human Neutrophils and Monocyte Functions In Vitro.", *Federation of Clinical Immunology Societies Annual Meeting, San Francisco, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science), et al.
	Jul.	"In Vivo Tumor Inhibitory Effects of Arabinoxylan Rice Bran (MGN-3/biobran) on Ehrlich Carcinoma-Bearing Mice", *International Research Conference on Food and Cancer, Washington D.C., USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science), et al.
2006	Sep.	"Phytonutrient-Therapy and Immune System Support for Patients with Hormone-Refractory Prostate Cancer", *3rd Annual Anti-Aging Conference London 2006, London, UK,* Pfeifer B. (Aeskular Cancer Centre)

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2005	May	"Improving effect of hydrolyzed rice bran on diabetic rats given high-carbohydrate feed", *The 59th Annual Meeting of the Japanese Society of Nutrition and Food Science, Tokyo, JAPAN* Kitamura N. and I. Ohara (Aichi Gakusen University), et al.
2004	Feb.	"Modified arabinoxylan rice bran (MGN-3/Biobran) potentiates apoptosis in cancer cells induced by multiple anti-cancer agents in vitro", *7th International Symposium on Predictive Oncology & Intervention Strategies, Nice,FRANCE,* Ghoneum M.(UCLA/Drew University of Medicine and Science), et al.
	Jun.	"Effect of the Oral Administration of Hydrolyzed Rice Bran (HRB) on the Common Cold Syndrome in the Elderly", *4th Conference of Japanese Society of Anti-Aging Medicine, Tokyo, JAPAN,* Omura K. (Dokkyo University School of Medicine), lchihashi K. {lchihashi Clinic), and K. Tazawa (Toyama Medical and Pharmaceutical University), et al.
	Jul.	"Modified arabinoxylan rice bran (MGN-3/Biobran), Potentiates Chemotherapy-induced Apoptosis in Human Breast Cencer Cells", *International Research Conference on Food, Nutrition and Cancer, Washington D.C., USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science), et al.
	Aug.	"The Oral Administration of Hydrolyzed Rice Bran Prevents the Common Cold Syndrome in the Elderly'' *21st Symposium of Medical and Pharmaceutical Society for WAKAN-YAKU, Toyama,JAPAN,* Omura K. (Dokkyo University School of Medicine, Department of Legal Medicine), lchihashi K. (lchihashi Clinic), Fujie T. (Atreju Uosaki), Kudo M., Zhu X.(Daiwa Pharmaceutical Co.,Ltd.), and K. Tazawa {Toyama Medical and Pharmaceutical University), et al.
	Aug.	"Evaluation of the Effect of Hydrolyzed Rice Bran on Reducing Respiratory Symptom in the Smokers" *21st Symposium of Medical and Pharmaceutical Society for WAKAN-YAKU, Toyama, JAPAN,* Omura K. (Dokkyo University School of Medicine, Department of Legal Medicine), Kudo M. (Daiwa Pharmaceutical Co., Ltd.) and N. Nakamichi {The Jikei University), N.S. Clinic, et al.
	Sep.	"Chemical Structure of lmmunostimulating Substances from Rice Bran", *2004 Annual Meeting of the Japanese Society of Applied Glycoscience and 12th Symposium on Amylases and Related Enzymes, Kagoshima, JAPAN,* Miura T. {Chiba M., Faculty of Education, Hirosaki University), Miyazaki Y. and Y. Kato (Hirosaki University, School of Medicine), et al.
	Sep.	"Hydrolyzed Rice Bran Reduces the Aggravation of Protein Metabolism in the Streptozotocin-lnduced Diabetic Rats", *American College of Nutrition, 45th Annual Meeting (Journal of American College of Nutrition Vol. 23, No. 5), Long Beach, USA,* Kitamura N. and I. Ohara (Aichi Gakusen University), et al.
	Nov.	"lmmunomodulatory Activity of Enzyme-treated Rice Bran Hemicellulose", *Japanese Association for Dietary Fiber Research, Chiba, JAPAN,* Miura T. (Hirosaki University, School of Medicine) and Y. Kato (Faculty of Education, Hirosaki University), et al.
	Feb.	"Modified arabinoxylan rice bran (MGN-3/Biobran) potentiates apoptosis in cancer cells induced by multiple anti-cancer agents in vitro", *7th International Symposium on Predictive Oncology & Intervention Strategies, Nice, FRANCE,* Ghoneum M.(UCLA/Drew University of Medicine and Science), et al.
	Jun.	"Effect of the Oral Administration of Hydrolyzed Rice Bran (HRB) on the Common Cold Syndrome in the Elderly", *4th Conference of Japanese Society of Anti-Aging Medicine, Tokyo, JAPAN,* Omura K. (Dokkyo University School of Medicine), lchihashi K. {lchihashi Clinic), and K. Tazawa (Toyama Medical and Pharmaceutical University), et al.

2003	Oct.	"A Novel Approach to Breast Cancer Therapy: Modified Arabinoxylan Rice Bran (MGN-3/BioBran) Enhances Apoptosis of Human Breast Cancer Cells Following Phagocytosis of Sacchromyces Cerevisiae, the Baker's Yeast, in vitro" *American Association for Cancer Research, Huntington Beach, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science), et al.
	Oct.	"lmmunoactivation therapy for various progressive cancers using rice bran arabinoxylan derivative (Bio Bran)", *The Japanese Society for Complementary and Alternative Medicine, Sendai, JAPAN,* Tsunekawa H. {Tsunekawa Gastrointestinal Clinic and Tokai Holistic Medical Foundation), et al.
	Dec.	"The effect in the physiological function of a Modified Arabinoxylan Rice Bran" *Japanese Society for Biotherapy, Toyama, JAPAN,* Masada M. {Chiba University) and K. Tazawa {Toyama Medical and Pharmaceutical University), et al.
2003	Dec.	"Effect of Rice Bran Arabinoxylan and Shark Lipid Extract on Complementary and Alternative Therapy", *7th Conference of Japanese Association for Alternative, Complementary and Traditional Medicine (JACT), Kobe, JAPAN,* Omori T. (Ginza San Espero Omori Clinic)

2002	Mar.	"Study on the growth inhibiting component of cancerous cells in culture cell lines derived from modified rice-bran arabinoxylan", *46th Japan Society for Bioscience, Biotechnology, and Agrochemistry, Sendai, JAPAN*, Miyazaki F. {Chiba University Graduate School of Science and Technology), Hashizume T. (Technology Department, Kazami Co., Ltd.), Kodama H., and M. Masada (Faculty of Horticulture, Chiba University), et al.

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	Mar.	"The effect of modified rice-bran arabinoxylan on NK activity of human peripheral blood lymphocytes " *46th Japan Society for Bioscience, Biotechnology, and Agrochemistry, Sendai, JAPAN,* Shimomura C. (Chiba University Graduate School of Science and Technology), Ueda Y., Kodama H., and M. Masada (Faculty of Horticulture, Chiba University) , et al.
	Oct.	"Normalization of the Lymphocyte System in Peripheric Blood Reaction by Arabinoxylan from Rice Bran (MGN-3)", *43rd Annual Meeting, American College of Nutrition, San Antonio, USA,* Ueda Y., and M. Masada (Faculty of Horticulture, Chiba University), et al.
	Oct.	"MGN-3 potentiates death receptor-induced apoptosis in cancer cells", *93rd Annual Meeting 2003 of American Association for Cancer Research, Boston, USA*, Ghoneum M. (UCLNDrew University of Medicine and Science)
	Nov.	"Effect of Enzyme-processed Rice Bran Hemicellulose (MGN-3) on Experimental Liver Dysfunction in Rats", *7th Conference of Japanese Association for Dietary Fiber Research, Tokyo, JAPAN,* Yamada T., Daizou A., Poindoglun K. (Chiba University Graduate School of Science and Technology), Egashira Y. and H. Sanada (Faculty of Horticulture, Chiba University), et al.
	Nov.	"Significance of asthmatic mouse model exposed to antigen {Toluene Diisocyanate) for a prolonged period", *52nd Conference of Japanese Society of Allergology, Yokohama, JAPAN,* Kanbayashi H. and Y. Endo (Department of Pathological Molecular Medicine, McMaster University)
	Nov.	"A new approach to regulating cytokine production", *The 1st International Symposium of The Institute of Functional Biomaterials and Biotechnology, Seoul, KOREA,* Nonoyama S. (National Defence Medical College)

2001	Mar.	"MGN-3, a Novel Antitumor Agent" *92nd Annual Meeting, American Association for Cancer Research, New Orleans, USA*, Uyemura K. (Drew University of Medicine and Science), et al.
	Jul.	"Inhibitory effect of MGN-3 on the progress of atopic dermatitis in NC mice", *11th International Congress of Immunology, Stockholm, SWEDEN*, Nonoyama S. (Tokyo Medical and Dental University)
	Nov.	"A Descriptive Questonnaire-Based Study on the Use of BioBran (MGN-3), in Chronic Fatigue Syndrome", *TOWNSEND LETTER for Doctors & Patients,* No. 220, November 2001 Kenyon J. {The Dove Clinic for Integrated Medicine)

2000	Jan.	"One Sizeable Step for Immunology, One Giant Leap for Cancer Patients", *TOWNSEND LETTER for Doctors & Patients,* No. 198, January 2000, Ghoneum M. (UCLNDrew University of Medicine and Science)
	Jun.	"The Effect of MGN-3 on Cisplatin and Adriamycin Induced Toxicity in the Rat" *American Society for Pharmacology and Experimental Therapeutics, Boston, USA,* Jacoby H., Wnorowski G. (Product Safety Labs), and K. Sakata (Creative Strategy Inc.), et al.
	Oct.	"Inhibitory effects of MGN-3 (modified Arabinoxylan from rice bran) on free radical", *The 59th Annual Meeting of the Japanese Cancer Association, Yokohama , JAPAN,* Saito T., Ohkami H., Tsukada K. {Toyama Medical and Pharmaceutical University, Surgery 2), Tazawa K., Namikawa H., Oida S., Koike J., Yatsuzuka M. (Toyama Medical and Pharmaceutical University, Adult nursing), and M. Masada (Chiba University), et al.
	Nov.	"Evaluation of Immune (Arabinoxylan) therapy seen from NK cell activity and the CD4/CD8 ratio on cancer patients", *The 3rd Annual Meeting of the Japanese Society for Complementary & Alternative Medicine & Treatment, Tokyo, JAPAN,* Takahara K. (Cancer Rescue Clinic Tokyo), et al.
	Dec.	"Natural Biological Response Modifier (MGN-3) Shown To Be Effective Against Tumor Cell Growth" *8th International Congress on Anti-Aging & Biomedical Technologies, Las Vegas, USA,* Ghoneum M. (UCLNDrew University of Medicine and Science)

1999	Jul.	"A case study of supplementary application of rice bran Arabinoxylan (MGN-3) to bone metastasis from lung cancer", *2nd Conference of Japanese Association for Alternative, Complementary and Traditional Medicine (JACT), Tokyo, JAPAN,* Sobajima T. (Hoshigaoka Welfare Annuity Hospital), et al.
	Jul.	"Evaluation of MGN-3 (Bio Bran) on Superoxide Scavenging Activity", *6th Japanese Conference on Cancer Prevention, Tokyo, JAPAN,* Tazawa K. (Toyama Medical and Pharmaceutical University), et al.
	Sep	"Modified Rice Bran Improves Glucose Tolerance in NIDDM Adult Rats Given Streptozocin as Neonates" *Journal of The American College of Nutrition,* Vol. 18, No. 5, Washington D.C., USA Ohara I. and K. Onai (Kobe Women's University), et al.

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	Dec.	"Evaluation of MGN-3 (Bio Bran) with activation function of NK cell activity on Superoxide Scavenging Activity" *12th Japanese Conference on Bio Therapy, Yokohama, JAPAN,* Tazawa K. (Toyama Medical and Pharmaceutical University), et al.
	Dec.	"Application of Modified Rice Bran Dietary Fiber to Diabetes and Taste Preference in reptozotocin-lncluded Diabetic Rats", *2nd International Conference on Food Factors, Kyoto, JAPAN,* Ohara I. and K. Onai {Laboratory of Nutrition, Faculty of Home Economics, Kobe Women's University), et al.
	Dec.	"lmmunostimulation and Cancer Prevention", *7th International Congress on Anti-Aging & Biomedical Technologies, Las Vegas,* USA Ghoneum M. (UCLNDrew University of Medicine and Science)

1998	Jun.	"MGN-3 lmmunotherapy for the Treatment of Cancer", *The First International Symposium on Disease Prevention by IP6 & Other Rice Components, Kyoto, JAPAN,* Ghoneum M. (UCLA/Drew University of Medicine and Science), et al.
	Aug.	"Human NK Activity and Synergism of a low dose of IL2a and a Modified Rice Bran Arabinoxylan on a Generation of TNFa" *Conference of Anti-Aging Mechanism, NJ, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science), et al.
	Sep.	"NK cell activity by MGN-3", *26th Academy of Alternative Medicine of Cancer, Los Angeles*, USA Ghoneum M. (UCLA/Drew University of Medicine and Science)
	Oct.	"lmmunopotentiation by utilization of MGN-3 tissue" *Congress on Anti-Aging Medicine, Reno, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science)
	Dec.	"Active oxygen radical scavenging activity of the plant polysaccharide processed foodstuff BioBran" *3rd JsoFF Conference, Tokyo, JAPAN,* Tazawa K.(Toyama Medical and Pharmaceutical University),et al.
	Dec.	"NK lmmunorestoration of Cancer Patients by MGN-3, a Modified Arabinoxylan Rice Bran (Study of 32 patients up to 4 years)", *6th International Congress on Anti-Aging & Bio-Medical Technologies, Las Vegas, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science)

1997	Sep.	"The Effect of MGN-3, an Arabinoxylan Compound, on Serum Lipids in Streptozotocin Induced Diabetic Rats." *38th American Meeting of Nutrition Annual Meeting, New York, USA,* Ohara I. (Kobe Women's University), et al.

1996	Apr.	"NKimmunomodulatoryfunction in27 cancer patients byMGN-3,a modified arabinoxylan fromricebran" *87th Annual Meeting of the American Association for Cancer Research (AACR), Washington* D.C., USA Ghoneum M. (UCLA/Drew University of Medicine and Science)
	Jun.	"Effect of human Natural Killer Cell activity and Interferon- *r* synthesis in vitro" *ASBMB/ASIP/AAI JOINT MEETING, New Orleans, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science)
	Jul.	"Anti HIV activity by MGN-3 in vitro" *11th International AIDS Conference, Vancouver, CANADA Ghoneum M.* (UCLA/Drew University of Medicine and Science)

1995	Mar.	Daiwa established the extraction technology of a new physiologically active substance "MGN-3" (rice bran Arabinoxylan compound) in rice bran. *The basic tests on MGN-3 started.*
	Nov.	"lmmunomodulatory and Anti-Cancer Properties of MGN-3, a modified xylose from rice bran, in 5 Patients with Breast Cancer" *An AACR Special Conference, Baltimore, USA,* Ghoneum M. (UCLA/Drew University of Medicine and Science)

1992	Apr.	Daiwa commenced development in the area of functional foods. *A cooperative study with Professor Mamdooh Ghoneum of UCLA / Drew University of Medicine and Science started.*

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Ghoneum M. 1998. "Anti-HIV Activity *in Vitro* of MGN-3, an Activated Arabinoxylan from Rice Bran", *BBRC,* Vol. 243, pp. 25-29.

Ghoneum M. and J. Brown. 1999. "NK lmmunorestration of Cancer Patients by MGN-3, A Modified Arabinoxylan Rice Bran (Study of 32 Patients Followed for up to 4 years)", *Anti-Aging Medical Therapeutics,* Vol. Ill, pp.217-226.

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Endo Y. and H. Kanbayashi. 2003. "Modified Rice Bran Beneficial for Weight Loss of Mice as a Major and Acute Adverse Effect of Cisplatin", *Pharmacology and Toxicology,* Vol. 92, pp. 300-303.

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