PRAXIS 321
FUNKTIONELLE MEDIZIN
& KINDERHEILKUNDE

Liebe Eltern, Familienangehörige, Freunde und Betroffene,

Vielleicht habt ihr einen Vortrag von mir gehört oder ein Interview des Online Kongress „Down Syndrom – leicht.er.leben“ mit mir gesehen. Vielleicht hattet ihr davor noch nichts von TNI (Targeted Nutritional Intervention, die Behandlung des Down Syndroms mit Nahrungsergänzungsmitteln) gehört und wollt Euch nun näher darüber informieren. Vielleicht hattet Ihr zwar schon von TNI gehört, Euch jedoch bisher nicht getraut, dies für Eure Kinder, Familienmitglieder oder Freunde anzuwenden, da die meisten Ärzte der Behandlung eher negativ gegenüberstehen und Euch bisher nicht weiterhelfen konnten. Oder Ihr habt schon intensive Erfahrungen mit TNI gesammelt und sucht nach Studien, die positive Ergebnisse einer Behandlung zeigen konnten, damit ihr diese Information mit Euren Ärzten und Therapeuten oder auch Freunden und Familienmitgliedern teilen könnt. Vielleicht habt Ihr auch schon mit Euren Ärzten über TNI gesprochen und als Antwort erhalten, dass es keine ausreichenden wissenschaftlichen Studien zu diesem Thema gäbe.

In jedem Fall hoffe ich, dass die nachfolgende Zusammenfassung der genetischen, biochemischen und metabolischen Besonderheiten des Down Syndroms für Euch hilfreich ist. **Gedacht ist die folgende Zusammenfassung um sie mit Euren Ärzten und Therapeuten zu teilen; es wird daher ein gewisses Grundverständnis von Genetik und Biochemie vorausgesetzt.** Das Kongress-Interview bzw. mein Vortrag konnten hoffentlich einen verständlichen Überblick über das komplexe Thema geben.

Mir liegt das Thema TNI sowohl als Mutter einer Tochter mit Down Syndrom als auch besonders als Heilpraktikerin und Wissenschaftlerin sehr am Herzen und ich wünsche mir für Menschen mit Trisomie 21, dass Ihre medizinischen Besonderheiten endlich (an)erkannt und entsprechend behandelt werden, damit einem langen, gesunden und glücklichen Leben nichts (oder deutlich weniger) im Wege steht.

Ich stehe jederzeit gerne für Fragen zu Verfügung und freue mich, Eure Kinder in meiner Praxis begrüßen zu dürfen.

Beste Grüße,
Eure Petra Buchanan

PS: Bitte gebt die folgenden Seiten als Information weiter und behaltet diese Seite für Euch.

Dr. rer. nat. Petra Buchanan
Heilpraktikerin
Stechertweg 29
79104 Freiburg
0761/38 488 944
info@praxis321.de
www.praxis321.de

Übersicht über die biologischen Grundlagen für die Behandlung einer Trisomie 21 mittels Targeted Nutritional Intervention (TNI)

Sehr geehrte Ärzte und Kollegen,

Eventuell wurden Sie von den Eltern eines Patienten nach Nahrungsergänzungsmitteln zur Behandlung des Down Syndroms gefragt. Nachfolgend stelle ich zusammenfassend die genetischen und biochemischen Besonderheiten einer Trisomie 21 dar, die als Grundlage für eine Behandlung mittels Targeted Nutritional Intervention (TNI) dient, um Sie mit dem aktuellen Stand der wissenschaftlichen Forschung vertraut zu machen.

Teil 1 beschreibt die komplexe Genetik sowie Epigenetik einer Trisomie 21, sowie die daraus folgenden biochemischen und metabolischen Veränderungen. Teil 2 erwähnt einige gängige Nahrungsergänzungsmittel, die bei Down Syndrom bisher erforscht wurden und Teil weiterer Studien sind, sowie Teil 3 eine Übersicht empfehlenswerter Labortests. Teil 4 ist ein annotiertes Literaturverzeichnis, mit Studien zur Behandlung des Down Syndroms.

Teil 1: Die genetischen, epigenetischen und biochemischen Besonderheiten einer Trisomie 21

Trisomie 21 tritt mit einer Inzidenz von ca. 1:600 Geburten auf. Ein großer Teil der Schwangerschaften mit einem extra Chromosom 21 führt bereits im ersten oder zweiten Trimester zu einem Abort (bis zu 80 %[1]), da wie bei vielen anderen Trisomien auch das zusätzliche genetische Material zu Veränderungen führt, die nicht mit dem Leben vereinbar sind. Es konnte jedoch gezeigt werden, dass das Genom von Menschen mit Trisomie 21 vergleichsweise wenige schädliche Mutationen enthält, um das Ungleichgewicht der Aneuploidie auszugleichen[1].

Obwohl Down Syndrom 1866 symptomatisch von **John Langdon H. Down** beschrieben wurde, konnte erst **Jérôme Lejeune** 1959 zeigen, dass die Ursache für das Syndrom in einer extra Kopie des Chromosom 21 liegt. Die Sequenz dieses Chromosoms wurde im Jahre 2000 veröffentlicht und ca. **225 Gene** darauf beschrieben[2]. Aus Studien mit partiellen Trisomien weiß man, dass nur ein kleiner Teil des Chromosoms 21 tatsächlich die Symptome des Down Syndroms induziert, dies wird als sogenannte **Down Syndrome Critical Region (DSCR)** bezeichnet, in der 40 Gene liegen[3,4]. Die „minimale“ DSCR wird jedoch weiterhin kontrovers diskutiert und ist Bestandteil intensiver Forschung. Es ist mittlerweile auch bekannt, dass sich, obwohl nur wenige Gene in dieser Region liegen, die Auswirkungen des extra Chromosoms 21 nicht auf dieses beschränken, sondern genomweit erstrecken[5]. Es konnte weiterhin gezeigt werden, dass es sehr viele nicht-kodierende Abschnitte auf Chromosom 21 gibt, darunter fünf sogenannte **microRNAs (miRNA)**, die insgesamt über **3600 Gene** auf anderen Chromosomen regulieren können[6,7].

Das weite Spektrum der individuellen Ausprägung des Down Syndroms lässt sich nicht ausschließlich durch einen simplen **Gendosis-Effekt** erklären (die Syntheserate für ein Genprodukt richtet sich nach der Anzahl der zuständig Allele; bei Trisomie 21 sind alle auf Chromosom 21

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

liegenden Gene nicht in doppelt, sondern in dreifacher Ausführung vorhanden; damit kann die Produktion **150 %** anstelle von 100 % erreichen), sondern auch durch **epigenetische Veränderungen**[8,9,10]. Diese stellen **reversible** Veränderungen in der Genexpression dar, die nicht auf einer veränderten DNA-Sequenz beruhen, sondern Mechanismen wie **DNA-Methylierung** und **Histon-Modifikationen** beinhalten. Das humane **Epigenom** ist also theoretisch lebenslang flexibel veränderbar, z.B. durch Umwelteinflüsse, Medikamente, Ernährung und Emotionen. Damit bietet sich auch ein interessantes Behandlungsfenster um die erhöhte Gendosis, die das extra Chromosom hervorruft, wieder auszugleichen.

Eine solche Behandlung stellt die sogenannte **Targeted Nutritional Intervention (TNI)** dar, die viele Eltern für ihre Kinder mit Down Syndrom verwenden[11]; diese versucht mehrere der grundlegend gestörten biochemischen Stoffwechselwege auszugleichen. Unter anderem werden Gene wie **SOD1** (Superoxiddismutase 1), **RCAN1** (Regulator of Calcineurin 1), **CBS** (Cystathionine Beta Synthase), **DYRK1A** (Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A), **APP** (Amyloid Beta Precursor Protein), **MAPT** (Microtubule-associated protein tau), **COLVI** (Collagen Type VI), **CREB** (cAMP Responsive Element Binding Protein), **MECP2** (Methyl-CpG Binding Protein 2), **HRF** (Histamine Release Factor), **S100B** (S100 Calcium Binding Protein B), **miRNA-155** gezielt angegriffen. Die betroffenen Stoffwechselwege betreffen den systemischen **oxidativen Stress**, den **Folsäurestoffwechsel** und die **Methylierung**, die **mitochondriale Dysfunktion**, den **Kollagenstoffwechsel**, den **Histaminmangel** im Gehirn, den **Acetylcholinstoffwechsel**, sowie die vorzeitige Entwicklung des **Alzheimers**. Eine TNI Behandlung stellt *keine* Heilung dar und versucht auch nicht die Persönlichkeit des Betroffenen zu verändern, sondern die jeweiligen besonderen biochemischen Bedürfnisse zu erfüllen.

Aus vielen persönlichen Gesprächen mit betroffenen Eltern weiß ich, dass Ärzte häufig angeben, dass es „keine ausreichende Forschung“ bzw. „keine Studien“ zum Thema Behandlung der Trisomie 21 gäbe und dass diese als genetische Erkrankung grundsätzlich nicht behandelbar sei. Gemeint sind fehlende doppelblinde, randomisierte klinische Studien mit Menschen mit Trisomie 21. Es gibt jedoch unzählige peer-reviewed, veröffentlichte mechanistische Studien, sowie präklinische und translationale Studien, die zum einen die biochemischen Stoffwechselwege und metabolischen Dysbalancen der Trisomie 21 identifiziert haben und die zum anderen deutliche positive Effekte einer Behandlung mit Stoffen, die in diese Stoffwechselvorgänge eingreifen, gezeigt haben (siehe Teil 3). Das grundlegende Ziel einer Behandlung der Trisomie 21 ist es also, die gestörte Biochemie so weit wie möglich zurück auf Normalniveau zu bringen.

Warum gibt es nur wenige klinische Studien? Die oben dargestellte genetische und epigenetische Komplexität des Down Syndroms und die damit verbundene hohe individuelle Variabilität machen deutlich, dass es bei Weitem nicht so einfach ist, sinnvolle klinische Studien in diesem Bereich durchzuführen. Kurzfristige doppelblinde, randomisierte klinische Studien mit einzelnen Inhibitoren oder Antioxidantien können nur schwer signifikant positive Effekte zeigen, zumindest nicht als messbare Änderungen der „Intelligenz“ oder „Meilensteine der Entwicklung“. Eine häufig zitierte Studie die keine messbaren Auswirkungen auf die Mengen an oxidativem Stress

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

und die Entwicklung feststellen konnte, testete in niedrigen Dosierungen Selen, Zink, Vitamin A/C/E, in Kombination mit Folinsäure an vier Monate alte Säuglingen[12]. Die Behandlung erfolgte über 18 Monate. Die Autoren erwähnen jedoch in der Diskussion, dass die gewählten Dosierungen eventuell nicht ausreichend waren, um die Biochemie tatsächlich zu beeinflussen.

Das bestmögliche Fenster einer effektiven Behandlung stellt die **pränatale Entwicklung** dar, da hier ein früher Ausgleich der genetischen Dysbalance die größten Auswirkungen haben kann[13]. Eine Behandlung der Trisomie 21 zu einem späteren Zeitpunkt müsste jedoch, um signifikante Effekte in doppelblinden, randomisierten klinischen Studien geben zu können, **möglichst viele der kritischen Gene** des Chromosoms 21 erfassen und **nicht nur einzelne biochemische Pathways**; dies ist bisher jedoch nicht der Fall gewesen. Zusätzlich müssten auch entsprechende Grundkrankheiten wie Hypothyreodismus, obstruktive Schlafapnoe und ein möglicher Wachstumshormonmangel in die klinischen Studien mit einbezogen werden, da diese häufig mit einer Trisomie 21 assoziiert sind und ebenfalls deutlichen Einfluss auf die kindliche Entwicklung haben[14,15,16,17]. Geforscht wird zusätzlich am „**Silencing**“ des gesamten extra Chromosoms 21 (Mechanismus ähnlich dem zweiten X-Chromosom bei Frauen), welches *in vitro* bereits geglückt ist[18] und in der Zukunft eine mögliche Heilung des Down Syndroms sein könnte.

Was sind die **Risiken** einer Behandlung mit TNI? Grundsätzlich muss diese **individualisiert** werden und entsprechende regelmäßige **Blutkontrollen** sollten durchgeführt werden (dies sollte mit der medizinischen Grundversorgung eines Down Syndroms durch den Kinderarzt gegeben sein[19]), um eine mögliche Überdosierung frühzeitig zu erkennen. Da sich die Level an systemischem oxidativem Stress sowohl im Blut als auch im Urin unkompliziert nachweisen lassen und andere Parameter z.B. des Folsäurestoffwechsels (MCV, Homocystein, Folat), der Schildrüsenfunktion (TSH, freie T4/T3 Werte, sowie reverser T3), eine gestörte Zink/Kupfer Balance, sowie Ferritin, Vitamin D3, und Lipidwerte ebenfalls einfach messbar sind, kann damit die Dosierung entsprechend optimiert werden. Es muss dabei jedoch beachtet werden, dass die sogenannten **Dietary Reference Values (DRVs)** „die Menge eines bestimmten Nährstoffes angeben, die regelmäßig aufgenommen werden muss, um die Gesundheit in einem ansonsten **gesunden** Individuum (oder Population) zu erhalten“[20]. Diese errechneten Mengen variieren zwischen Individuen (auch Gesunden) unter anderem aufgrund der genetischen und epigenetischen Unterschiede (sowie Alter, Geschlecht, verschiedene Stressoren wie Infektion oder Trauma) und kann nicht automatisch mit dem Bedarf einer aneuploiden Population mit deutlich veränderter Biochemie gleichgesetzt werden.

Die Risiken der TNI Behandlung sollten auch im Vergleich mit den **Langzeitschäden** eines extra 21. Chromosoms betrachtet werden: Eine 20-Jahres follow-up Studie konnte zeigen, dass über **97 %** der Studienteilnehmer eine **Demenz** mit einem durchschnittlichen Diagnosealter von 55 Jahren entwickeln[21]. Die entsprechenden **Neuropathologien** (Alzheimer Plaques und Neurofibrillen) lassen sich jedoch schon deutlich früher im Gehirn nachweisen. Da Menschen mit Down Syndrom durch die bessere prä- und perinatale Betreuung und Operationsmöglichkeiten (z.B. schwerer Herzfehler) heute eine deutlich höhere Lebenserwartung haben (sie stieg in Europa von durchschnittlich neun Jahren (1929) auf ca. 60 Jahre (2004) an; etliche erreichen heute das 70. Lebensjahr), stellt die **vorzeitige Alterung** und die **frühe Entwicklung des Alzheimers** ein ernst zu

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

nehmendes Problem dar[22]. Zahlreiche Studien haben gezeigt, dass die Ursache hierfür zumindest teilweise der erhöhte oxidative Stress ist, welcher durch TNI reduziert wird[23].

Es ist Zeit kritisch zu hinterfragen, ob eine **umfassende biochemische und metabolische Behandlung** der Trisomie 21 aufgrund limitierter klinischer Studien grundsätzlich abgelehnt werden sollte, obwohl es heute zahlreiche mechanistische Studien gibt, welche die gestörte Biochemie aufgeschlüsselt haben. Menschen mit Down Syndrom haben durch ihre positive Grundeinstellung, Offenheit und Kreativität ein großes Potential einen wichtigen Beitrag zu unserer Gesellschaft zu leisten; sie führen ein erfülltes Leben[24] und haben ein Recht auf adäquate medizinische Betreuung. Es darf auch nicht übersehen werden, dass die steigende Anzahl an **pharmakologischen Studien** bisher nur limitierten Erfolg hatte, effektive Behandlungen zur Verbesserung der Lebensqualität von Menschen mit Trisomie 21 zu identifizieren[24]. Eine Behandlung mit TNI sollte daher frühzeitig in Betracht gezogen werden.

1. Popadin K. et al. Slightly deleterious genomic variants and transcriptome perturbations in Down syndrome embryonic selection. Genome Res. 2018 Jan;28(1):1-10.
2. Hattori M. et al. The DNA sequence of human chromosome 21. Nature. 2000 May 18;405(6784):311-9.
3. Toyoda A. et al. Comparative genomic sequence analysis of the human chromosome 21 Down syndrome critical region. Genome Res. 2002 Sep;12(9):1323-32.
4. di Cunto F. and Berto G. Molecular Pathways of Down Syndrome Critical Region Genes. http://dx.doi.org/10.5772/53000
5. Letourneau A. Domains of genome-wide gene expression dysregulation in Down's syndrome. Nature. 2014 Apr 17;508(7496):345-50.
6. Zhao Y. A microRNA cluster (let-7c, miRNA-99a, miRNA-125b, miRNA-155 and miRNA-802) encoded at chr21q21.1-chr21q21.3 and the phenotypic diversity of Down's syndrome (DS; trisomy 21). J Nat Sci. 2017 Sep;3(9). pii: e446.
7. Shapshak P. Molecule of the month: miRNA and Down's syndrome. Bioinformation. 2013; 9(15): 752–754.
8. Karmiloff-Smith A. et al, The importance of understanding individual differences in Down syndrome. Version 1. F1000Res. 2016; 5: F1000 Faculty Rev-389.
9. Dekker AD. et al, Epigenetics and Down Syndrome. Neuropsychiatric Disorders and Epigenetics, pp.163-184, 2016.
10. Henneman P. et al. Widespread domain-like perturbations of DNA methylation in whole blood of Down syndrome neonates. PLoS One. 2018 Mar 30;13(3):e0194938.
11. Lewanda AF. et al, Patterns of Dietary Supplement Use in Children with Down Syndrome. J Pediatr 2018;201:100-5.
12. Ellis, JM. et al. Supplementation with antioxidants and folinic acid for children with Down's syndrome: randomised controlled trial. BMJ. 2008 Mar 15; 336(7644): 594–597.
13. Guedj et al. Prenatal treatment of Down syndrome: a reality? Curr Opin Obstet Gynecol. 2014 Apr;26(2):92-103.
14. King K. et al. Thyroid dysfunction in children with Down syndrome: a literature review. Ir J Med Sci. 2014 Mar;183(1):1-6.
15. Simpson R. et al. Obstructive sleep apnea in patients with Down syndrome: current perspectives.Nat Sci Sleep. 2018 Sep 13;10:287-293.
16. Annerén G. et al. Growth hormone therapy in young children with Down syndrome and a clinical comparison of Down and Prader-Willi syndromes. Growth Horm IGF Res. 2000 Apr;10 Suppl B:S87-91.
17. Capone GT. et al. Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines. Am J Med Genet A. 2018 Jan;176(1):116-133.
18. Jiang J. et al. Translating Dosage Compensation to Trisomy 21. Nature. 2013 Aug 15; 500(7462): 296–300.
19. https://www.awmf.org/uploads/tx_szleitlinien/027-051l_S2k_Down-Syndrom-Kinder-Jugendliche_2016-09.pdf

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

20. EFSA (European Food Safety Authority), 2017. Dietary reference values for nutrients: Summary report. EFSA supporting publication 2017:e15121. 92 pp.
21. McCarron M. et al. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. J Intellect Disabil Res. 2017 Sep;61(9):843-852.
22. Cipriani G. et al, Aging With Down Syndrome: The Dual Diagnosis: Alzheimer's Disease and Down Syndrome.Am J Alzheimers Dis Other Demen. 2018 Jun;33(4):253-262.
23. Lott IT. Antioxidants in Down syndrome. Biochim Biophys Acta. 2012 May;1822(5):657-63.
24. Hart SJ. et al. Pharmacological interventions to improve cognition and adaptive functioning in Down syndrome: Strides to date. Am J Med Genet A. 2017 Nov;173(11):3029-3041.
25. Skotko BG. et al. Self-perceptions from people with Down syndrome. Am J Med Genet A. 2011 Oct;155A(10):2360-9.

Dr. rer. nat. Petra Buchanan
Heilpraktikerin
Stechertweg 29
79104 Freiburg
0761/38 488 944
info@praxis321.de
www.praxis321.de

Teil 2: Nahrungsergänzungmittel, die bei Trisomie 21 erforscht wurden

Studien, welche die nachfolgenden Nahrungsergänzungsmittel unterstützen, sind in Teil 4 aufgeführt.

1. **Multivitamin/-mineral Nutrivene D** (speziell für Down Syndrom formuliert): Enthält Vitamine, Mineralien und Aminosäuren in einer Konzentration, welche die erhöhte Expression etlicher Gene bei Trisomie 21 regulieren soll. Das Produkt ist individualisierbar (über ein Rezept können z.B. Selen oder Zink entfernt/reduziert werden).
2. **EGCG (Epigallocatechin-3-gallate/Grüntee-Extrakt):** Ein Catechin, welches die Expression des DYRK1a Gens beeinflusst und die Funktion der Mitochondrien verbessert; soll die Neurogenese stimulieren. Wirkt als Antioxidans und anti-inflammatorisch. Soll das Gedächtnis positiv beeinflussen.
3. **Resveratrol (Polyphenol):** Inhibiert microRNA-155, welche bei Down Syndrom überexprimiert ist und damit sowohl die Blut-Hirn-Schranke als auch die Permeabilität der Darmschleimhaut negativ beeinflussen soll. Diese microRNA führt auch zu Störungen des Immunsystems und Autoimmunerkrankungen. Resveratrol soll weiterhin die Neurogenese stimulieren und als Antioxidans die Funktion der Mitochondrien verbessern.
4. **Curcumin:** Soll die Neurogenese stimulieren; wirkt anti-inflammatorisch und als Antioxidans. Soll die Bildung von beta-Amyloid Plaques reduzieren. Die *Longvida*-Form soll eine höhere Bioverfügbarkeit haben und in der Lage sein, die Blut-Hirn-Schranke zu überwinden.
5. **PQQ (Pyrroloquinolinequinone):** Fängt überschüssige Superoxid-Radikale ab; damit wird die Menge an systemischem oxidativen Stress reduziert und bestehende Mitochondrien geschützt. Soll die Neubildung von Mitochondrien fördern. Soll über CREB-Erhöhung die Expression von RCAN1 reduzieren. Soll Peroxynitrite reduzieren, ein Toxin welches mit TAU und Amyloid Proteinen fusioniert und damit zur Bildung von Alzheimer Plaques führt.
6. **DHA/EPA:** Wichtig für die allgemeine Gehirnentwicklung, das Nervensystem und die Neurogenese (steigert den Neuriten-Auswuchs; schützt vor Inflammation und Oxidation, erhöht BDNF und hat allgemein neuroprotektive Eigenschaften).
7. **Antioxidantien:**
   - **Glutathion:** „Master Antioxidans"; meist zu niedrig bei Trisomie 21 aufgrund SOD1/CBS; es wird die reduzierte Form (*Setria*) benötigt.
   - **Vitamin C:** Antioxidans; kann die Funktion der Nebennieren verbessern, wirkt anti-viral.
   - **Vitamin A und E:** Antioxidantien.
   - **Melatonin** (verschreibungspflichtig): Antioxidans; besonders wirksam auf die Mitochondrien. Normalisiert die gestörten Schlafzyklen.
   - **Lycopin und Quercetin:** Sollen RCAN1 reduzieren, sowie die Amyloid-beta induzierte Apoptose von Neuronen inhibieren.
   - **CoQ10:** Soll die allgemeine Funktion der Mitochondrien unterstützen.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

8. **Papaya und Mango:** Sollen über den Histamine-Release factor (HRF) die Menge an Histamin im Gehirn erhöhen, welche normalerweise zu niedrig ist.
9. **Piracetam** (verschreibungspflichtig): Ist ein Nootropikum; soll beim Transport vom Sauerstoff in die Zellen helfen, Neuronen vor Oxidation schützen und beim Erhalt einer funktionsfähigen Lipidschicht der Zellen helfen (bei DS durch die vorzeitige Alterung gestört). Soll sich positiv auf das Lernen und das Gedächtnis auswirken und die Verbindung der beiden Hemisphären des Gehirns verbessern.
10. **Zink:** Unterstützt das Immunsystem, Wundheilung, Wachstum, Schilddrüse.
11. **Selen:** Wichtig für normale Schilddrüsen Funktion; erhöht Glutathion Peroxidase.
12. **Vitamin D3:** Immunsystem, Knochenstoffwechsel, erhöht Glutathion Peroxidase.

Teil 3: Labortests zur Überprüfung der Behandlung mit TNI

Vor TNI Start	Nach TNI Start	Zusätzlich möglich
Großes Blutbild	Vitamin A	Cortisol (vor 9.00 Uhr)
Ferritin, Zink, Kupfer, Selen	Vitamin E	DHEA-S
Folsäure	Vitamin B1	HbA1c
Vitamin B12, HoloTC	Vitamin B6	Jod
Vitamin D (als 25-OH-Vit. D)		Magnesium (im Erthrozyten)
Homocystein		Leberwerte und Nierenwerte
CRP sensitiv		Histamin
Blutfettwerte (Cholesterin gesamt, HDL, LDL, Triglyzeride)		Kreatinin
Komplettes Schilddrüsen Panel: TSH, T4 frei, T3 frei, reverses T3 and Antikörper		Zöliakie Screen (Deamidierte Gliadinpeptide IgA/IgG, Transglutaminase IgA/IgG, sowie HLA-DQ zur Risikoeinschätzung)
Oxidativer Stress: Lipidperoxide/oxidiertes LDL		

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

Teil 4: Studien zu Veränderungen der Biochemie, des Metabolismus und Immunsystems bei Menschen mit Trisomie 21

A. Besonderheiten der Biochemie und des Metabolismus bei Trisomie 21

1. Brás A. et al. Down syndrome and microRNAs. Biomed Rep. 2018 Jan;8(1):11-16.
   "This overexpression may contribute to the neuropathology, congenital heart defects, leukemia and low rate of solid tumor development observed in patients with DS. MiRNAs located on other chromosomes and with associated target genes on or off chromosome 21 may also be involved in the DS phenotype."
2. Buonuomo PS. et al. Lipid profiles in a large cohort of Italian children with Down syndrome. Eur J Med Genet. 2016 Aug;59(8):392-5.
   "Since dyslipidemia is a modifiable risk factor, identification may play a central role in prevention of CVD." "In addition, obesity and diabetes are more frequent in DS children and have to be considered potential comorbidities that increase CVD risk. One-third to one-half of children with DS are overweight, and this is true in our population with DS. So, the presence of a less favorable lipid profile may represent an additional risk factor." "... routine lipid screening should be suggested in children (with DS as in the general population), during periodic health controls beginning from the age of 2 yrs, and specific secondary preventive strategies ranging from changing the diet to low-fat-diet to pharmacologic intervention may be considered."
3. Caracausi M. et al. Plasma and urinary metabolomic profiles of Down syndrome correlate with alteration of mitochondrial metabolism. Sci Rep. 2018 Feb 14;8(1):2977.
   "Multivariate analysis of the NMR metabolomic profiles showed a clear discrimination (up to of 80% accuracy) between the DS and the control groups. The univariate analysis of plasma and urine revealed a significant alteration for some interesting metabolites. Remarkably, most of the altered concentrations were consistent with the 3:2 gene dosage model, suggesting effects caused by the presence of three copies of Hsa21 rather than two: DS/normal ratio in plasma was 1.23 (pyruvate), 1.47 (succinate), 1.39 (fumarate), 1.33 (lactate), 1.4 (formate). Several significantly altered metabolites are produced at the beginning or during the Krebs cycle." "Thinking of DS as a metabolic disease would result in a change of perspective, especially from the point of view of possible treatment. The focus must be shifted from what is upstream (gene excess or gene defect) to what is downstream (gene product). The "blocked" mechanism that determines ID severity and specific molecule protagonists of this complex mechanism might be identified, as occurred for other complex diseases: "Phenylketonuria, galactosemia, vitamine B6 dependant homocystinuria, to take few examples, can be properly handled and the children protected against mental deficiency. Who could believe that during the coming years no new progress will be achieved?"
4. Carratelli et al. Reactive oxygen metabolites and prooxidant status in children with Down's syndrome. Int J Clin Pharmacol Res. 2001;21(2):79-84.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"Reactive oxygen species were significantly higher in children with Down's syndrome than in controls. Total antioxidant capacity was significantly higher in controls than in children with Down's syndrome. Therefore, children with Down's syndrome have to cope with a significant prooxidant environment. Oxidative stress causes alterations such as atherosclerosis, early aging, immunological default and neurologic disorders in Down's syndrome patients."

5. Cenini G. et al. Association between frontal cortex oxidative damage and beta-amyloid as a function of age in Down syndrome. Biochim Biophys Acta. 2012 Feb;1822(2):130-8.

   "These results suggest that oxidative damage, but not nitrosative stress, may contribute to the onset and progression of AD pathogenesis in DS. Conceivably, treatment with antioxidants may provide a point of intervention to slow pathological alterations in DS."

6. de Haan JB. et al. An altered antioxidant balance occurs in Down syndrome fetal organs: implications for the "gene dosage effect" hypothesis. J Neural Transm Suppl. 2003;(67):67-83.

   "We examined the SOD1 (Cu/Zn-superoxide dismutase-1) to GPX1 (glutathione peroxidase-1) mRNA ratio in individual organs, as both enzymes form part of the body's defense against oxidative stress, and because a disproportionate increase of SOD1 to GPX1 results in noxious hydroxyl radical damage. All organs investigated show an approximately 2-fold increase in the SOD1 to GPX1 mRNA ratio. We propose that it is the altered antioxidant ratio that contributes to certain aspects of the DS phenotype."

7. de San Martin JZ. et al. GABAergic over-inhibition, a promising hypothesis for cognitive deficits in Down syndrome. Free Radic Biol Med. 2018 Jan;114:33-39.

   "Learning and memory impairments linked to intellectual disabilities in DS could result from synaptic plasticity deficits and excitatory-inhibitory alterations leading to changes in neuronal circuitry in the brain of affected individuals. Increasing number of studies in mouse and cellular models converge towards the assumption that excitatory-inhibitory imbalance occurs in DS, likely early during development. Thus increased inhibition appears to be a common trend that could explain synaptic and circuit disorganization."

8. de Toma I., et al. Where Environment Meets Cognition: A Focus on Two Developmental Intellectual Disability Disorders. Neural Plast. 2016; 2016: 4235898.

   "We speculate that epigenetic drugs, such as EGCG in combination with other cognitive enhancers and specific drugs interfering with the cell and disorder specific molecular targets, will allow the recovery of the epigenetic balance lost in IDDs such as DS and FXS, making the healing of the cognitive impairment possible."

9. Garcez ME. et al. Oxidative stress and hematologic and biochemical parameters in individuals with Down syndrome. Mayo Clin Proc. 2005 Dec;80(12):1607-11.

   "… increases in seric superoxide dismutase and catalase activities were observed in people with Down syndrome. Although other studies are necessary, our results add to the understanding of the mechanisms responsible for the increased oxidative stress observed in

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

individuals with Down syndrome and may be useful in supporting future antioxidant therapies that will improve the lives of people with Down syndrome."

10. Garlet TR. et al. Systemic oxidative stress in children and teenagers with Down syndrome. Life Sci. 2013 Oct 11;93(16):558-63.

"The present study showed that the presence of trisomy 21 in children and adolescents results in significant biochemical changes that contribute to a systemic and exacerbated oxidative stress in the blood of DS patients, in a way similar to that already demonstrated by our group in other chronic diseases where oxidative stress is highlighted."

11. He J. et al. Plasma antioxidant enzymes and lipoperoxidation status in children with Down syndrome. Clin Biochem. 2016 Jan;49(1-2):61-5.

"Oxidative stress (OS) may play a critical role in cell aging and neurologic disorders that are often seen in Down syndrome (DS) patients. ...Abnormal redox metabolism takes place in DS individuals. Reducing glutathione peroxidase may be a compensatory mechanism of protection against intracellular OS. Moreover, monitoring of decreases in glutathione peroxidase activity may be a useful biomarker for evaluating OS in DS patients."

12. Horvath S. et al. Accelerated epigenetic aging in Down syndrome. Aging Cell. 2015 Jun;14(3):491-5.

"Down Syndrome (DS) entails an increased risk of many chronic diseases that are typically associated with older age. The clinical manifestations of accelerated aging suggest that trisomy 21 increases the biological age of tissues, but molecular evidence for this hypothesis has been sparse. Here, we utilize a quantitative molecular marker of aging (known as the epigenetic clock) to demonstrate that trisomy 21 significantly increases the age of blood and brain tissue"

13. Ichinohe A. et al. Cystathionine beta-synthase is enriched in the brains of Down's patients. Biochem Biophys Res Commun. 2005 Dec 23;338(3):1547-50.

"Cystathionine beta-synthase (CBS) is encoded on chromosome 21 and deficiency in its activity causes homocystinuria, the most common inborn error of sulfur amino acid metabolism and characterized by mental retardation and vascular disease. Here, we show that the levels of CBS in DS brains are approximately three times greater than those in the normal individuals. …The over-expression of CBS may cause the developmental abnormality in cognition in DS children and that may lead to AD in DS adults."

14. Kim SH. et al. Human brain cytosolic histamine-N-methyltransferase is decreased in Down syndrome and increased in Pick's disease. Neurosci Lett. 2002 Mar 22;321(3):169-72.

"Decreased HMT in DS would be compatible with findings of decreased histamine synthesis, thus reflecting a compensation mechanism to antagonize reduced synthesis by decreased degradation."

15. Kim SH. et al. Decreased brain histamine-releasing factor protein in patients with Down syndrome and Alzheimer's disease. Neurosci Lett. 2001 Mar 2;300(1):41-4.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"Histamine-releasing factor (HRF) stimulates secretion of histamine that is widely distributed in brain and released as neurotransmitter. Several studies suggested that histaminergic deficits could contribute to the cognitive decline in Alzheimer's disease (AD). Based upon deranged histamine metabolism in brain of patients with AD and Down Syndrome (DS), we

aimed to study HRF in brain of AD and DS. We used two-dimensional gel electrophoresis, matrix-assisted laser desorption ionization mass spectroscopy and specific software to quantify HRF. HRF was significantly reduced in temporal cortex, thalamus and caudate nucleus of DS and in temporal cortex of AD as compared to controls. This is the first report to show decreased HRF brain levels in DS and AD suggesting the explanation for the decreased cognitive function in neurodegenerative/dementing disorders."

16. Lejeune J. Pathogenesis of mental deficiency in trisomy 21. Am J Med Genet Suppl. 1990;7:20-30.

    "The interest of regulating thyroid metabolism, when needed, is exemplified. Reequilibration of monocarbon metabolism is discussed and the seemingly favourable effect of folinic acid medication in pseudo-Alzheimer complication is presented."

17. Leng RX. et al. Role of microRNA-155 in autoimmunity. Cytokine Growth Factor Rev. 2011 Jun;22(3):141-7.

    "Recently, aberrant expression of miR-155 was observed in many autoimmune conditions, including rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE). Moreover, functional analysis demonstrated that miR-155 has powerful regulatory potential in a wide variety of immune cells through targeting specific mRNAs. Since pathogenic immune cells play a pivotal role in pathogenesis of human autoimmune diseases, miR-155 might be a versatile therapeutic target."

18. Lopez-Ramirez MA. et al. MicroRNA-155 negatively affects blood-brain barrier function during neuroinflammation. FASEB J. 2014 Jun;28(6):2551-65.

    "We propose that brain endothelial miR-155 is a negative regulator of BBB function that may constitute a novel therapeutic target for CNS neuroinflammatory disorders."

19. Lu J. et al. S100B and APP promote a gliocentric shift and impaired neurogenesis in Down syndrome neural progenitors. PLoS One. 2011;6(7):e22126.

    "Ongoing inflammation through APP and S100B overexpression further promotes a gliocentric HNPs (human neural progenitors) phenotype. Thus, the loss in neuronal numbers seen in DS is not merely due to increased HNPs cell death and neurodegeneration, but also a fundamental gliocentric shift in the progenitor pool that impairs neuronal production."

20. Meguid et al. Evaluation of superoxide dismutase and glutathione peroxidase enzymes and their cofactors in Egyptian children with Down's syndrome. Biol Trace Elem Res. 2001 Jul;81(1):21-8.

    "Our results showed that in the population with complete trisomy 21 and translocations, Cu/Zn superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities were increased, whereas in cases with mosaicism, the enzymes activities were within normal

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

limits. Plasma copper concentrations were increased, whereas whole-blood selenium concentrations were significantly decreased in the three DS groups. Plasma zinc levels were within normal in all patients. Our results are useful tools for identifying nutritional status and guiding antioxidant intervention."

21. Mircher C. et al. Variation of amino acids in relation to age in Down syndrome subjects. Arch Pediatr. 1997 Nov;4(11):1093-9.

    "Two major changes were found in Down's syndrome: a decrease in plasma concentration of serine at any age, which could be due to a dosage effect of cytathionine-beta-synthase, and an increase in plasma lysine concentration in patients above 10 year's old, probably due to premature aging. Other minor changes were also present in plasma and urine, also possibly explained by premature aging."

22. Pastore A. et al. Glutathione metabolism and antioxidant enzymes in children with Down syndrome. J Pediatr. 2003 May;142(5):583-5.

    "Oxidative stress has been proposed as a pathogenic mechanism of atherosclerosis, cell aging, and neurologic disorders in Down syndrome. This study demonstrates a systemic decrease of all glutathione forms, including glutathionyl-hemoglobin, in the blood of children with Down syndrome. Furthermore, we obtained a disequilibrium, in vivo, between the antioxidant enzyme activities."

23. Peiris H. et al. RCAN1 regulates mitochondrial function and increases susceptibility to oxidative stress in mammalian cells. Oxid Med Cell Longev. 2014;2014:520316.

    "This study demonstrates that increasing Regulator of Calcineurin 1 (RCAN1) expression alters mitochondrial function and increases the susceptibility of neurons to oxidative stress in mammalian cells. These findings further contribute to our understanding of RCAN1 and its potential role in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease and Down Syndrome."

24. Porta S. et al. RCAN1 (DSCR1) increases neuronal susceptibility to oxidative stress: a potential pathogenic process in neurodegeneration.Hum Mol Genet. 2007 May 1;16(9):1039-50.

    "Regulator of Calcineurin 1 (RCAN1 or DSCR1) is a dose-sensitive gene whose overexpression has been linked to Down syndrome (DS) and Alzheimer's disease (AD) neuropathology and to the response of cells to stress stimuli. Here, we show that RCAN1 mRNA and protein expression are sensitive to oxidative stress (OS) in primary neurons, and we evaluate the involvement of RCAN1 dosage in neuronal death induced by OS." "These findings highlight the importance of RCAN1 gene dosage in the modulation of cell survival and death pathways and suggest that changes in the amount of RCAN1 could represent an important mechanism for regulating susceptibility to neurodegeneration, especially in DS and AD."

25. Sanchez-Mut JV. et al. Human DNA methylomes of neurodegenerative diseases show common epigenomic patterns.Transl Psychiatry. 2016 Jan 19;6:e718.

    "The DNA methylation landscapes obtained show that neurodegenerative diseases share similar aberrant CpG methylation shifts targeting a defined gene set. Our findings suggest

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

that neurodegenerative disorders might have similar pathogenetic mechanisms that subsequently evolve into different clinical entities. The identified aberrant DNA methylation changes can be used as biomarkers of the disorders and as potential new targets for the development of new therapies."

26. Schneider C., et al. Similar deficits of central histaminergic system in patients with Down syndrome and Alzheimer disease. Neurosci Lett. 1997 Feb 7;222(3):183-6.

"…we observed a significant decrease of histamine levels in the DS group. Histamine levels in AD brains tended to be decreased. Histidine concentrations and HMT activities were comparable between the three groups. Thus, our results for the first time show histaminergic deficits in brains of patients with DS resembling the neurochemical pattern in AD. Neuropathological changes may be responsible for similar neurochemical alterations of the histaminergic system in both dementing disorders."

27. Shichiri M. The role of lipid peroxidation in neurological disorders. J Clin Biochem Nutr. 2014 May;54(3):151-60.

"…lipid peroxidation is involved in neurological disorders, including Alzheimer's disease, Parkinson's disease, stroke, and Down Syndrome (DS). There are few clinical reports about the efficacy of antioxidants for neurological disorders. It is considered that the timing to start antioxidants therapy is important. As our report about the effectiveness of α-tocopherol administration to the fetuses of DS mouse, antioxidants therapy before appearance of symptoms may be effective against these neurological disorders. In order to start a treatment in early stages, biomarkers which can be used to diagnose in early stages of each neurological disorders are required."

28. Stagni F. et al. Neurogenesis impairment: An early developmental defect in Down syndrome. Free Radic Biol Med. 2018 Jan;114:15-32.

"Although many triplicated genes may be involved, in the light of the studies reviewed here, DYRK1A, APP, RCAN1 and OLIG1/2 appear to be particularly important determinants of many neurodevelopmental alterations that characterize DS because their triplication affects both the proliferation and fate of neural precursor cells as well as apoptotic cell death. Based on the evidence reviewed here, pathways downstream to these genes may represent strategic targets, for the design of possible intervention."

29. Sullivan KD, et al. Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation. Scientific Reports 7, Article number: 14818 (2017).

"We recently identified an activated interferon response associated with trisomy 21 (T21) in human cells of different origins, consistent with overexpression of the four interferon receptors encoded on chromosome 21, and proposed that DS could be understood partially as an interferonopathy. ()… we employed proteomics approaches to analyze blood samples from 263 individuals, 165 of them with DS, leading to the identification of dozens of proteins that are consistently deregulated by T21. Most prominent among these proteins are

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

numerous factors involved in immune control, the complement cascade, and growth factor signaling. Importantly, people with DS display higher levels of many pro-inflammatory cytokines (e.g. IL-6, MCP-1, IL-22, TNF-α) and pronounced complement consumption, resembling changes seen in type I interferonopathies and other autoinflammatory conditions. Therefore, these results are consistent with the hypothesis that increased interferon signaling caused by T21 leads to chronic immune dysregulation, and justify investigations to define the therapeutic value of immune-modulatory strategies in DS."

30. Zhang Y. et al. Aberrations in circulating inflammatory cytokine levels in patients with Down syndrome: a meta-analysis. Oncotarget. 2017 Sep 19;8(48):84489-84496.
    "Taken together, these results demonstrated that patients (children) with Down Syndrome (DS) are accompanied by increased circulating cytokine tumor necrosis factor-α, IL-1β and interferon-γ levels, strengthening the clinical evidence that patients (children) with DS are accompanied by an abnormal inflammatory response."
31. Zis et al. Memory decline in Down syndrome and its relationship to iPF2alpha, a urinary marker of oxidative stress.PLoS One. 2014 Jun 5;9(6):e97709.
    "Change in iPF2alpha over time may have potential as a biomarker for memory decline in Down syndrome and potentially also help to track progression of MCI to AD in the general population."

B. Studien zum Thema Acetylcholin und Neutrotransmitter

1. Blusztajn JK. et al. Neuroprotective Actions of Dietary Choline. Nutrients. 2017 Jul 28;9(8).
   "Choline is an essential nutrient for humans. It is a precursor of membrane phospholipids (e.g., phosphatidylcholine (PC)), the neurotransmitter acetylcholine, and via betaine, the methyl group donor S-adenosylmethionine. High choline intake during gestation and early postnatal development in rat and mouse models improves cognitive function in adulthood, prevents age-related memory decline, and protects the brain from the neuropathological changes associated with Alzheimer's disease (AD), and neurological damage associated with epilepsy, fetal alcohol syndrome, and inherited conditions such as Down and Rett syndromes. These effects of choline are correlated with modifications in histone and DNA methylation in brain, and with alterations in the expression of genes that encode proteins important for learning and memory processing, suggesting a possible epigenomic mechanism of action. Dietary choline intake in the adult may also influence cognitive function via an effect on PC containing eicosapentaenoic and docosahexaenoic acids; polyunsaturated species of PC whose levels are reduced in brains from AD patients, and is associated with higher memory performance, and resistance to cognitive decline."
2. Gray SL. et al. Higher cumulative anticholinergic use is associated with an increased risk for dementia. JAMA Intern Med. 2015 Mar;175(3):401-7.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

„Efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time."

3. Fodale V. et al. The cholinergic system in Down's syndrome. J Intellect Disabil. 2006 Sep;10(3):261-74.

   "… these data potentially support the therapeutic use of drugs that are principally administered to improve severe learning difficulties in cases of Alzheimer's and Parkinson's diseases in patients with Down's syndrome. Consequently, cognitive and learning dysfunctions in patients with Down's syndrome should not be considered and accepted today as unavoidable and untreatable symptoms of this syndrome"

4. Godridge H. et al. Alzheimer-like neurotransmitter deficits in adult Down's syndrome brain tissue. J Neurol Neurosurg Psychiatry. 1987 Jun; 50(6): 775–778.

   "The results indicate profound transmitter deficits and neuropathological abnormalities in adult patients with Down's syndrome, which closely resemble those of Alzheimer's disease."

5. Hasselmo ME. The Role of Acetylcholine in Learning and Memory. Curr Opin Neurobiol. 2006 December ; 16(6): 710–715.

   "In summary, there is increasing convergence of research on the role of acetylcholine in learning and memory. "

6. Tun MK. and Herzon SB. The pharmacology and therapeutic potential of (-)-huperzine A. J Exp Pharmacol. 2012 Sep 5;4:113-23.

   "The manifold pharmacological effects of (-)-huperzine A, especially when considered in the context of its favorable toxicity profile, argue for its development for the treatment of neurological disorders. Although further study is required to fully elucidate the precise mechanisms underlying these effects, available evidence suggests (-)-huperzine A is superior to many existing antineurodegenerative agents and may operate, in some instances, by orthogonal mechanisms."

7. Qian ZM. and Ke Y. Huperzine A: Is it an Effective Disease-Modifying Drug for Alzheimer's Disease? Front Aging Neurosci. 2014; 6: 216.

   "A growing body of evidence has demonstrated that Huperzine A (HupA) has multifaceted pharmacological effects. In addition to the symptomatic, cognitive-enhancing effect via inhibition of acetylcholinesterase, a number of recent studies have reported that this drug has "non-cholinergic" effects on Alzheimer's disease (AD). Most important among these is the protective effect of HupA on neurons against amyloid beta-induced oxidative injury and mitochondrial dysfunction as well as via the up-regulation of nerve growth factor and antagonizing N-methyl-d-aspartate receptors. The most recent discovery that HupA may reduce brain iron accumulation lends further support to the argument that HupA could serve as a potential disease-modifying agent for AD and also other neurodegenerative disorders by significantly slowing down the course of neuronal death."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

8. Wang R. et al. Progress in studies of huperzine A, a natural cholinesterase inhibitor from Chinese herbal medicine. Acta Pharmacol Sin. 2006 Jan;27(1):1-26.

   "Huperzine A (HupA), a novel alkaloid isolated from the Chinese herb Huperzia serrata, is a potent, highly specific and reversible inhibitor of acetylcholinesterase (AChE). Compared with tacrine, donepezil, and rivastigmine, HupA has better penetration through the blood-brain barrier, higher oral bioavailability, and longer duration of AChE inhibitory action. HupA has been found to improve cognitive deficits in a broad range of animal models. HupA possesses the ability to protect cells against hydrogen peroxide, beta-amyloid protein (or peptide), glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis. These protective effects are related to its ability to attenuate oxidative stress, regulate the expression of apoptotic proteins Bcl-2, Bax, P53, and caspase-3, protect mitochondria, upregulate nerve growth factor and its receptors, and interfere with amyloid precursor protein metabolism." "The phase IV clinical trials in China have demonstrated that HupA significantly improved memory deficits in elderly people with benign senescent forgetfulness, and patients with Alzheimer disease and vascular dementia, with minimal peripheral cholinergic side effects and no unexpected toxicity."

9. Zhang HY. New insights into huperzine A for the treatment of Alzheimer's disease. Acta Pharmacol Sin. 2012 Sep;33(9):1170-5.

   "This article reflects the research progress made in molecular pharmacology and pharmacological therapy for treating AD with huperzine A, showing that the classical cholinergic and potential non-cholinergic target of huperzine A may shed more light on the successes gained from huperzine A in the AD therapy. Accumulative evidence suggests that single target drug always exert limited clinical effects for AD therapy, while combined therapies or drugs with multi-pharmacological activities would be a promising future therapeutic approach to address the varied pathological aspects of the disease. "

C. Studien zum Thema Alzheimer, Gehirn und Neurodegeneration

1. Bagheri S. et al.. Role of Copper in the Onset of Alzheimer's Disease Compared to Other Metals.Front Aging Neurosci. 2017; 9: 446.

   "The root of copper deficiency in the brain cells seems to be an important factor in AD. Since it is accompanied by copper enrichment in lipid rafts, one can argue that an elevation in lipid raft domains could lead to copper deficiency in the brain, thus targeting lipid rafts could be an effective therapeutic approach. Indeed, some data show that disrupting lipid rafts (by omega-3 fatty acids) delays the incidence of the disease."

2. Barone E. et al. HNE-modified proteins in Down syndrome: Involvement in development of Alzheimer disease neuropathology. Free Radic Biol Med. 2017 Oct;111:262-269.

   "The neuropathology of DS involves multiple molecular mechanisms, similar to AD, including the deposition of beta-amyloid (Aβ) into senile plaques and tau hyperphosphorylation in neurofibrillary tangles. Interestingly, many genes encoded by chromosome 21, in addition

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

to being primarily linked to amyloid-beta peptide (Aβ) pathology, are responsible for increased oxidative stress (OS) conditions that also result as a consequence of reduced antioxidant system efficiency. However, redox homeostasis is disturbed by overproduction
of Aβ, which accumulates into plaques across the lifespan in DS as well as in AD, thus generating a vicious cycle that amplifies OS-induced intracellular changes. The present review describes the current literature that demonstrates the accumulation of oxidative damage in DS with a focus on the lipid peroxidation by-product, 4-hydroxy-2-nonenal (HNE). HNE reacts with proteins and can irreversibly impair their functions. We suggest that among different post-translational modifications, HNE-adducts on proteins accumulate in DS brain and play a crucial role in causing the impairment of glucose metabolism, neuronal trafficking, protein quality control and antioxidant response. We hypothesize that dysfunction of these specific pathways contribute to accelerated neurodegeneration associated with AD neuropathology."

3. Beyer K. et al. Cystathionine beta synthase as a risk factor for Alzheimer disease.Curr Alzheimer Res. 2004 May;1(2):127-33.

   "One of the known risk factors for developing Alzheimer disease (AD) is hyperhomocysteinemia. The latter may result from mutations of the genes coding for three key enzymes involved in homocysteine metabolism (methylenetetrahydrofolate reductase [MTHFR], methionine synthase [MS], and cystathionine beta-synthase [CBS])."

4. Bredesen DE. Reversal of cognitive decline: a novel therapeutic program. Aging (Albany NY). 2014 Sep;6(9):707-17.

   "The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes. Furthermore, given the failure of monotherapeutics in AD to date, the results raise the possibility that such a therapeutic system may be useful as a platform on which drugs that would fail as monotherapeutics may succeed as key components of a therapeutic system."

5. Brewer GJ. Alzheimer's disease causation by copper toxicity and treatment with zinc. Front Aging Neurosci. 2014; 6: 92.

   "We have (…) shown that AD patients are zinc deficient compared to age-matched controls. Because zinc is a neuronal protective factor, we postulate that zinc deficiency may also be partially causative of AD. We carried out a small 6 month double blind study of a new zinc formulation and found that in patients age 70 and over, it protected against cognition loss. Zinc therapy also significantly reduced serum free copper in AD patients, so efficacy may come from restoring normal zinc levels, or from lowering serum free copper, or from both."

6. Cole GM. et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobiol Aging. 2005 Dec;26 Suppl 1:133-6.

   "… identification of the phenolic anti-inflammatory/anti-oxidant compound curcumin, the yellow pigment in turmeric that we found targeted multiple AD pathogenic cascades. The

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

dietary omega-3 fatty acid, docosahexaenoic acid (DHA), also limited amyloid, oxidative damage and synaptic and cognitive deficits in a transgenic mouse model. Both DHA and curcumin have favorable safety profiles, epidemiology and efficacy, and may exert general anti-aging benefits (anti-cancer and cardioprotective)."

7. Frautschy SA. Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. Neurobiol Aging. 2001 Nov-Dec;22(6):993-1005.

   "Because of its low side-effect profile and long history of safe use, curcumin may find clinical application for AD prevention."

8. Jackson et al. Vitamin E and Alzheimer's disease in subjects with Down's syndrome. J Ment Defic Res. 1988 Dec;32 (Pt 6):479-84.

   "People with Down's syndrome (DS) are at high risk of developing Alzheimer's disease (AD). The gene coding for superoxide dismutase-/ on chromosome 21 resulting in excess activity of the enzyme with consequent risk of oxidative damage might account for the premature ageing. Vitamin E protects against such damage. Plasma vitamin E levels measured in 12 DS subjects with AD (8.19 +/- 0.77 micrograms/ml) were lower (P less than 0.05) than in 12 DS controls (9.43 +/- 1.57 micrograms/ml). It is suggested that there may be an interaction between risk of AD and the protective action of vitamin E."

9. Johnson EJ, Schaefer EJ. Potential role of dietary n-3 fatty acids in the prevention of dementia and macular degeneration. Am J Clin Nutr. 2006 Jun;83(6 Suppl):1494S-1498S.

   "Our own unpublished observations from the Framingham Heart Study suggest that > or =180 mg/d of dietary DHA (approximately 2.7 fish servings/wk) is associated with an approximately 50% reduction in dementia risk. At least this amount of DHA is generally found in one commercially available 1-g fish oil capsule given daily."

10. Kou X and Chen N. Resveratrol as a Natural Autophagy Regulator for Prevention and Treatment of Alzheimer's Disease. Nutrients. 2017 Sep; 9(9): 927.

    "In this review, the regulation of miRNAs and autophagy using resveratrol during the prevention and treatment of AD are systematically discussed, which will be beneficial to establish a target for the direct link between pharmacological intervention and AD in the future."

11. Landmark K. Could intake of vitamins C and E inhibit development of Alzheimer dementia? Tidsskr Nor Laegeforen. 2006 Jan 12;126(2):159-61.

    "Several observational studies in mostly healthy, elderly individuals have indicated that vitamin C and E, mainly from food as well as the combination of high doses of the same vitamins, may have beneficial effect on the development of Alzheimer dementia. One clinical controlled trial in patients with manifest Alzheimer dementia, in which vitamin E 2000 mg/day was given as the only vitamin, has to a certain extent confirmed these results.

    "A causal relationship between intake of the vitamins and Alzheimer dementia has not been clarified. The correct dosages are not known, but a diet rich in these vitamin could probably

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

reduce the risk of dementia. With a high intake of vitamin E, the addition of vitamin C is necessary."

12. Li DD. et al. Serum Copper, Zinc, and Iron Levels in Patients with Alzheimer's Disease: A Meta-Analysis of Case-Control Studies.Front Aging Neurosci. 2017 Sep 15;9:300.

    "The results of our meta-analysis provided rigorous statistical support for the association of the serum levels of metals and the risk of AD, suggesting a positive relationship between the serum copper levels and AD risk, and a negative relationship between the serum zinc/iron levels and AD risk."

13. Lockrow JP. et al. Age-related neurodegeneration and memory loss in down syndrome. Curr Gerontol Geriatr Res. 2012;2012:463909.

    "Down syndrome (DS) is a condition where a complete or segmental chromosome 21 trisomy causes variable intellectual disability, and progressive memory loss and neurodegeneration with age. DS leads to pathological hallmarks of Alzheimer's disease (AD) by 40 or 50 years of age. Inflammation and oxidative stress are early events in DS pathology, and focusing on these pathways may lead to development of successful intervention strategies for AD associated with DS. Here we discuss recent findings and potential treatment avenues regarding development of AD neuropathology and memory loss in DS."

14. Lott IT. and Head E. Down syndrome and Alzheimer's disease: a link between development and aging. Ment Retard Dev Disabil Res Rev. 2001;7(3):172-8.

    "A combination of factors may contribute to Alzheimer's disease (AD) in Down Syndrome (DS) including an overexpression of the APP leading to early and enhanced amyloid deposition. Further, the gene for superoxide dismutase, an enzyme involved with reducing oxidative damage in the brain is also on chromosome 21, suggesting the involvement of dysfunction in oxidative damage repair mechanisms in the development of pathology. This may be followed or exacerbated by immune system dysfunction intrinsic to DS and may be important in the accelerated accumulation of AD pathology after age 30 years."

15. Lott IT. Neurological phenotypes for Down syndrome across the life span. Prog Brain Res. 2012 ; 197: 101–121.

    "While all individuals have the characteristic neuropathology of Alzheimer's disease (AD) by age 40years, the prevalence of dementia is not universal. The tendency to develop AD is related, in part, to several genes on chromosome 21 that are overexpressed in DS. Intraneuronal accumulation of β-amyloid appears to trigger a cascade of neurodegeneration resulting in the neuropathological and clinical manifestations of dementia. Functional brain imaging has elucidated the temporal sequence of amyloid deposition and glucose metabolic rate in the development of dementia in DS. Mitochondrial abnormalities contribute to oxidative stress which is part of AD pathogenesis in DS as well as AD in the general population. A variety of medical comorbidities threaten cognitive performance including sleep apnea, abnormalities in thyroid metabolism, and behavioral disturbances."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

16. Mehta PD. et al,. Increased amyloid beta protein levels in children and adolescents with Down syndrome. J Neurol Sci. 2007 Mar 15;254(1-2):22-7.

"The over expression of APP gene in Down Syndrome (DS) leads to increases in plasma Abeta40 and Abeta42 levels before plaque formation in DS brain. Higher neopterin concentrations in DS reflect inflammatory cell activation."

17. Nunomura A. et al. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J Neuropathol Exp Neurol. 2000 Nov;59(11):1011-7.

"…in brains of patients with DS, increased levels of oxidative damage occur prior to the onset of Abeta deposition."

18. Nunomura A. et al. Involvement of oxidative stress in Alzheimer disease. J Neuropathol Exp Neurol. 2006 Jul;65(7):631-41.

"Contrary to the commonly held notion that pathologic hallmarks of Alzheimer's disease (AD) signify etiology, several lines of evidence now indicate that aggregation of amyloid-beta and tau is a compensatory response to underlying oxidative stress. Therefore, removal of proteinaceous accumulations may treat the epiphenomenon rather than the disease and may actually enhance oxidative damage. Although some antioxidants have been shown to reduce the incidence of AD, the magnitude of the effect may be modified by individual factors such as genetic predisposition (e.g. apolipoprotein E genotype) and habitual behaviors. Because caloric restriction, exercise, and intellectual activity have been

experimentally shown to promote neuronal survival through enhancement of endogenous antioxidant defenses, a combination of dietary regimen of low total calorie and rich antioxidant nutrients and maintaining physical and intellectual activities may ultimately prove to be one of the most efficacious strategies for AD prevention."

19. Ono K., et al. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro. J Neurosci Res. 2004 Mar 15;75(6):742-50.

"Although the mechanism by which Curcumin and rosmarinic acid (RA) inhibit beta-amyloid fibrils (fAbeta) formation from amyloid beta-peptide and destabilize preformed fAbeta in vitro remains unclear, they could be a key molecule for the development of therapeutics for AD."

20. Ono K. et al. Preformed beta-amyloid fibrils are destabilized by coenzyme Q10 in vitro. Biochem Biophys Res Commun. 2005 Apr 29;330(1):111-6.

"CoQ(10) dose-dependently inhibited beta-amyloid fibrils (fAbeta) formation from amyloid beta-peptide (Abeta), as well as their extension. Moreover, it destabilized preformed fAbetas. The anti-amyloidogenic effects of CoQ(10) were slightly weaker than those of NDGA and Myr. CoQ(10) could be a key molecule for the development of therapeutics for AD. Preformed beta-amyloid fibrils are destabilized by coenzyme Q10 in vitro."

21. Rafii MS. Pro: Are we ready to translate Alzheimer's disease modifying therapies to people with Down syndrome? Alzheimers Res Ther. 2014; 6(5): 60.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"Multiple lines of evidence suggest that individuals with DS suffer exactly the same pathological process in later life as individuals with the other forms of AD. Indeed, there is little to distinguish the pathological changes in either condition. In DS, triplication of the APP gene leads to the overproduction of Aβ and drives amyloidogenic pathways leading to plaques, tangles, and neurodegeneration. Owing to the 100% prevalence of AD pathology in adults with DS, individuals with DS represent a well-defined subgroup of predetermined AD."

22. Reddy PH. Protective Effects of Indian Spice Curcumin Against Amyloid-β in Alzheimer's Disease. J Alzheimers Dis. 2018;61(3):843-866.

"Recent research on Aβ and curcumin has revealed that curcumin prevents Aβ aggregation and crosses the blood-brain barrier, reach brain cells, and protect neurons from various toxic insults of aging and Aβ in humans."

23. Reddy VS. et al. A systematic review and meta-analysis of the circulatory, erythrocellular and CSF selenium levels in Alzheimer's disease: A metal meta-analysis (AMMA study-I). J Trace Elem Med Biol. 2017 Jul;42:68-75.

"This meta-analysis suggests that circulatory selenium concentration is significantly lower in AD patients compared to controls and this decrease in selenium is directly correlated with an important antioxidant enzyme, the GPx, in AD."

24. Subba RK. Mechanisms of disease: DNA repair defects and neurological disease. Nat Clin Pract Neurol. 2007 Mar;3(3):162-72.

"The current overall picture indicates that oxidative stress is a major causative factor in genomic instability in the brain, and that the nature of the resulting neurological phenotype depends on the pathway through which the instability is normally repaired."

25. Villaflores ON. et al. Curcuminoids and resveratrol as anti-Alzheimer agents. Taiwan J Obstet Gynecol. 2012 Dec;51(4):515-25.

"Alzheimer disease (AD) is by far the most common cause of dementia globally. This neurodegenerative disorder of the brain is chronic and progressive, characterized clinically by the deterioration in the key symptoms of behavioral and cognitive abilities. Treatment options for this disease currently are limited. Deposition of amyloid-β and tau hyperphosphorylation are cardinal pathologic features of AD that lead to the formation of neuronal plaques and neurofibrillary tangles, respectively. In addition to mounting research on herbal compounds for the treatment of AD, curcuminoids and resveratrol appear to be beneficial as anti-AD agents. Curcuminoids (curcumin and demethoxycurcumin) and resveratrol possess unique properties that make them especially worthy of further studies. This review article revisits and presents the current research done on the potential of the curcuminoids curcumin and demethoxycurcumin and the polyphenolic compound resveratrol as anti-AD compounds."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

26. Wilcock DM. and Griffin WS. Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis. J Neuroinflammation. 2013 Jul 16;10:84.

"The discovery of neuroinflammatory changes, including dramatic proliferation of activated glia overexpressing a chromosome 2 gene product--the pluripotent immune cytokine interleukin-1 (IL-1)--and a chromosome 21 gene product--S100B--in the brains of fetuses, neonates, and children with DS opened the possibility that early events in Alzheimer pathogenesis were driven by cytokines."

27. Wong H. et al. RCAN1 overexpression promotes age-dependent mitochondrial dysregulation related to neurodegeneration in Alzheimer's disease. Acta Neuropathol. 2015 Dec;130(6):829-43.

"Aging is the largest risk factor for Alzheimer's disease (AD). Patients with Down syndrome (DS) develop symptoms consistent with early-onset AD, suggesting that overexpression of chromosome 21 genes such as Regulator of Calcineurin 1 (RCAN1) plays a role in AD pathogenesis. RCAN1 levels are increased in the brain of DS and AD patients but also in the human brain with normal aging. RCAN1 has been implicated in several neuronal functions, but whether its increased expression is correlative or causal in the aging-related progression of AD remains elusive. We show that brain-specific overexpression of the human RCAN1.1S isoform in mice promotes early age-dependent memory and synaptic plasticity deficits, tau pathology, and dysregulation of dynamin-related protein 1 (DRP1) activity associated with mitochondrial dysfunction and oxidative stress, reproducing key AD features. Based on these findings, we propose that chronic RCAN1 overexpression during aging alters DRP1-mediated mitochondrial fission and thus acts to promote AD-related progressive neurodegeneration."

28. Wu S. et al. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. Neurosci Biobehav Rev. 2015 Jan;48:1-9.

"A higher intake of fish was associated with a lower risk of Alzheimer's disease (AD). However, there was no statistical evidence for similar inverse association between long-chain omega-3 fatty acids intake and risk of dementia or AD, nor was there inverse association between fish intake and risk of dementia."

29. Zhang Y. et al. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr. 2016 Feb;103(2):330-40.

"Fishery products are recommended as dietary sources and are associated with lower risk of cognitive impairment. Marine-derived DHA was associated with lower risk of dementia and AD but without a linear dose-response relation."

D. Studien zum Thema Antioxidantien

1. Ciaccio M. et al. Aminoacid profile and oxidative status in children affected by Down syndrome before and after supplementary nutritional treatment.Ital J Biochem. 2003 Jun;52(2):72-9.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"Although other studies must be performed to confirm and define such report, our experience supports the usefulness of a nutritional supplementation with aminoacids, vitamins and polyunsaturated fatty acids, also considering the absence of side effects."

2. Corrales A. et al. Long-term oral administration of melatonin improves spatial learning and memory and protects against cholinergic degeneration in middle-aged Ts65Dn mice, a model of Down syndrome. J Pineal Res. 2013 Apr;54(3):346-58.

   "Our results suggest that melatonin administration might improve the cognitive abilities of both TS and CO mice, at least partially, by reducing the age-related degeneration of basal forebrain cholinergic neurons. Thus, chronic melatonin supplementation may be an effective treatment for delaying the age-related progression of cognitive deterioration found in DS."

3. El-Bassyouni et al. Oxidative Stress -a Phenotypic Hallmark of Fanconi Anemia and Down Syndrome: The Effect of Antioxidants. Ann Med Health Sci Res. 2015 May-Jun;5(3):205-12.

   "Children with FA and DS had elevated levels of oxidative stress and more DNA damage than controls. Oxidative stress parameters and DNA damage improved in FA and DS patients after antioxidant administration. () Early administration of antioxidants to FA and DS patients is recommended for slowing of the disease course with symptoms amelioration and improvement of general health."

4. Gosh S. et al. Epigenomic maintenance through dietary intervention can facilitate DNA repair process to slow down the progress of premature aging. IUBMB Life. 2016 Sep;68(9):717-21.

   "DNA damage caused by various sources remains one of the most researched topics in the area of aging and neurodegeneration. Increased DNA damage causes premature aging. Aging is plastic and is characterised by the decline in the ability of a cell/organism to maintain genomic stability. Lifespan can be modulated by various interventions like calorie restriction, a balanced diet of macro and micronutrients or supplementation with nutrients/nutrient formulations such as Amalaki rasayana, docosahexaenoic acid, resveratrol, curcumin, etc. We propose here that agents or interventions that can maintain epigenomic stability and facilitate the DNA repair process can slow down the progress of premature aging, if not completely prevent it."

5. Lim S. et al. Lycopene inhibits regulator of calcineurin 1-mediated apoptosis by reducing oxidative stress and down-regulating Nucling in neuronal cells. Mol Nutr Food Res. 2017 May;61(5).

   "Lycopene inhibits RCAN1-mediated apoptosis by reducing reactive oxygen species (ROS) levels and by inhibiting NF-κB activation, Nucling induction, and the increase in apoptotic indices in neuronal cells. Consumption of lycopene-rich foods may prevent oxidative stress-associated neuronal damage in some pathologic conditions such as Down Syndrome or Alzheimer's disease."

6. Miles MV. et al. Coenzyme Q10 (ubiquinol-10) supplementation improves oxidative imbalance in children with trisomy 21. Pediatr Neurol. 2007 Dec;37(6):398-403.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"…this is the first study to indicate that the pro-oxidant state in plasma of children with trisomy 21, as assessed by ubiquinol-10:total coenzyme Q10 ratio, may be normalized with ubiquinol-10 supplementation."

7. Nachvak et al. α-Tocopherol supplementation reduces biomarkers of oxidative stress in children with Down syndrome: a randomized controlled trial. Eur J Clin Nutr. 2014 Oct;68(10):1119-23.

   "Down Syndrome (DS) children had greater levels of baseline oxidative stress than their siblings. Moreover, males had greater levels of 8OHdG than females but there was no significant association between age and biomarkers of oxidative stress. Although urinary 8OHdG concentrations decreased significantly in both α-tocopherol and alpha lipoic acid (ALA), groups compared with the baseline levels, mean final levels of urinary 8OHdG concentrations differed significantly only between α-tocopherol and placebo groups. () α-Tocopherol supplementation of the diets of DS children may attenuate oxidative stress at the DNA level."

8. Parisotto EB. et al. Antioxidant intervention attenuates oxidative stress in children and teenagers with Down syndrome. Res Dev Disabil. 2014 Jun;35(6):1228-36.

   "The daily antioxidant intervention with vitamins E and C during six months consistently attenuated the systemic oxidative insult promoted by trisomy 21 in children and teenagers."

9. Parisotto et al. Persistence of the benefit of an antioxidant therapy in children and teenagers with Down syndrome. Res Dev Disabil. 2015 Oct-Nov;45-46:14-20.

   "After the antioxidant supplementation, the activities of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GPx), glutathione reductase (GR), gamma-glutamyltransferase (GGT) and myeloperoxidase activity (MPO) were downregulated, while thiobarbituric acid reactive substances (TBARS) contents were strongly decreased, the contents of glutathione (GSH) and vitamin E were significantly increased, and no changes in G6PD and glutathione-S-transferase (GST) activity as well as in uric acid (UA) and protein carbonyls (PC) levels were detected. After the interruption of the antioxidant therapy for 6 months, DS patients showed elevated GPx and GGT activities and also elevated UA and TBARS levels. No changes in SOD, CAT, GR, GST, G6PD and MPO activities as well as in GSH, vitamin E, PC, TNF-α and IL-1β levels were detected. The results showed that the antioxidant intervention persistently attenuated the systemic oxidative damage in DS patients even after a relatively long period of cessation of the antioxidant intervention."

10. Parisotto EB. et al. Chronic Melatonin Administration Reduced Oxidative Damage and Cellular Senescence in the Hippocampus of a Mouse Model of Down Syndrome. Neurochem Res. 2016 Nov;41(11):2904-2913.

    "These results showed that this treatment attenuated the oxidative damage and cellular senescence in the brain of TS mice and support the use of melatonin as a potential therapeutic agent for age-related cognitive deficits and neurodegeneration in adults with DS."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

11. Reiter RJ.e t al. Melatonin as an antioxidant: biochemical mechanisms and pathophysiological implications in humans. Acta Biochim Pol. 2003;50(4):1129-46.

"Its successful use in human conditions where excessive free radical generation occurs, however, should encourage its continued use in the treatment of other disease processes, and there seem to be many, where oxidative stress is a component."

12. Sarkar PD. et al. Comparative analysis of lycopene in oxidative stress. J Assoc Physicians India. 2012 Jul;60:17-9.

"Dietary intake of tomato lycopene is beneficial to fight against oxidative stress (OS) but in the synthetic form it is more bioavailable and more effective against OS."

13. Tiano L. et al. Prolonged coenzyme Q10 treatment in Down syndrome patients: effect on DNA oxidation.Neurobiol Aging. 2012 Mar;33(3):626.e1-8.

"Our results highlight an age-specific reduction in the percentage of cells showing the highest amount of oxidized bases, indicating a potential role of CoQ(10) in modulating DNA repair mechanisms."

14. Uberos J. Melatonin and elimination of kynurenines in children with Down's syndrome. J Pediatr Endocrinol Metab. 2010 Mar;23(3):277-82.

"Patients with DS present levels of plasma melatonin and urinary kynurenine that are lower than the corresponding levels in the control population, together with higher values of kynurenic acid and anthranilic acid. These circumstances constitute an added risk to these patients of damage by free radicals."

15. Zaki ME. et al. Coenzyme Q10 and pro-inflammatory markers in children with Down syndrome: clinical and biochemical aspects. J Pediatr (Rio J). 2017 Jan - Feb;93(1):100-104.

"Interleukin 6 and tumor necrosis factor α levels in young children with Down syndrome may be used as biomarkers reflecting the neurodegenerative process in them. Coenzyme Q10 might have a role as a good supplement in young children with Down syndrome to ameliorate the neurological symptoms."

E. Studien zum Thema Grüntee Extrakt (EGCG)

1. de la Torre R. et al. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2016 Jul;15(8):801-810.

"Early cognitive intervention is the only routine therapeutic approach used for amelioration of intellectual deficits in individuals with Down's syndrome, but its effects are limited. We hypothesised that administration of a green tea extract containing epigallocatechin-3-gallate (EGCG) would improve the effects of non-pharmacological cognitive rehabilitation in young adults with Down's syndrome." "EGCG and cognitive training for 12 months was significantly more effective than placebo and cognitive training at improving visual recognition memory, inhibitory control, and adaptive behaviour."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

2. Guedj F. et al. Green tea polyphenols rescue of brain defects induced by overexpression of DYRK1A. PLoS One. 2009;4(2):e4606.

   "Individuals with partial HSA21 trisomies and mice with partial MMU16 trisomies containing an extra copy of the DYRK1A gene present various alterations in brain morphogenesis. They present also learning impairments modeling those encountered in Down syndrome. … DYRK1A is involved, during development, in the control of brain volume and cell density of specific brain regions. Gene dosage correction induces a rescue of the brain volume alterations. DYRK1A is also involved in the control of synaptic plasticity and memory consolidation. Increased gene dosage results in brain morphogenesis defects, low BDNF levels and mnemonic deficits in these mice. Epigallocatechin gallate (EGCG) - a member of a natural polyphenols family, found in great amount in green tea leaves - is a specific and safe DYRK1A inhibitor. We maintained control and transgenic mice overexpressing DYRK1A on two different polyphenol-based diets, from gestation to adulthood. The major features of the transgenic phenotype were rescued in these mice."

3. Ohishi T. et al. Anti-inflammatory Action of Green Tea. Antiinflamm Antiallergy Agents Med Chem. 2016;15(2):74-90.

   "Since green tea and EGCG have multiple targets and act in a pleiotropic manner, we may consider their usage to improve the quality of life in patients with inflammatory disease. Green tea and EGCG have beneficial health effects and no severe adverse effects; however, care should be taken to avoid overdosage, which may induce deleterious effects including hepatic injury.

4. Stagni F. et al. Epigallocatechin gallate: A useful therapy for cognitive disability in Down syndrome? Neurogenesis (Austin). 2017 Feb 2;4(1):e1270383.

   "Neurodevelopmental alterations and cognitive disability are constant features of Down syndrome (DS), a genetic condition due to triplication of chromosome 21. DYRK1A is one of the triplicated genes that is thought to be strongly involved in brain alterations. Treatment of Dyrk1A transgenic mice with epigallocatechin gallate (EGCG), an inhibitor of DYRK1A, improves cognitive performance, suggesting that EGCG may represent a suitable treatment of DS. Evidence in the Ts65Dn mouse model of DS shows that EGCG restores hippocampal development, although this effect is ephemeral. Other studies, however, show no effects of treatment on hippocampus-dependent memory. On the other hand, a pilot study in young adults with DS shows that EGCG transiently improves some aspects of memory. Interestingly, EGCG plus cognitive training engenders effects that are more prolonged. Studies in various rodent models show a positive impact of EGCG on brain and behavior, but other studies show no effect. In spite of these discrepancies, possibly due to heterogeneity of protocols/timing/species, EGCG seems to exert some beneficial effects on the brain. It is possible that protocols of periodic EGCG administration to individuals with DS (alone or in conjunction with other treatments) may prevent the disappearance of its effects."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

5. Vacca RA, Valenti D. Green tea EGCG plus fish oil omega-3 dietary supplements rescue mitochondrial dysfunctions and are safe in a Down's syndrome child. Clin Nutr. 2015 Aug;34(4):783-4.

   "This report may support clinical trials with these nutraceutics as potential therapeutic tool to prevent energy deficit-associated DS clinical signs."

6. Valenti D. et al. Epigallocatechin-3-gallate prevents oxidative phosphorylation deficit and promotes mitochondrial biogenesis in human cells from subjects with Down's syndrome. Biochim Biophys Acta. 2013 Apr;1832(4):542-52.

   "Previous studies from our group demonstrated in DS cells a decreased capacity of the mitochondrial ATP production system and overproduction of reactive oxygen species (ROS) in mitochondria. In this study we have tested the potential of epigallocatechin-3-gallate (EGCG) - a natural polyphenol component of green tea - to counteract the mitochondrial energy deficit found in DS cells. We found that EGCG, incubated with cultured lymphoblasts and fibroblasts from DS subjects, rescued mitochondrial complex I and ATP synthase catalytic activities, restored oxidative phosphorylation efficiency and counteracted oxidative stress." "In addition, EGCG strongly promoted mitochondrial biogenesis in DS cells. EGCG treatment promises thus to be a therapeutic approach to counteract mitochondrial energy deficit and oxidative stress in DS."

7. Weinreb O. et al. Neuroprotective molecular mechanisms of (2)-epigallocatechin-3-gallate: a reflective outcome of its antioxidant, iron chelating and neuritogenic properties. Genes Nutr (2009) 4:283–296.

   "Accumulating evidence suggests that oxidative stress, resulting in reactive oxygen species generation, plays a pivotal role in neurodegenerative diseases, supporting the implementation of radical scavengers and metal chelating agents, such as natural tea polyphenols, for therapy. Vast epidemiology data indicate a correlation between occurrence of neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases, and green tea consumption. In particular, recent literature strengthens the perception that diverse molecular signaling pathways, participating in the neuroprotective activity of the major green tea polyphenol, (-)-epigallocatechin-3-gallate (EGCG), renders this natural compound as potential agent to reduce the risk of various neurodegenerative diseases."

8. Wyganowska-Świątkowska M. et al. Can EGCG Alleviate Symptoms of Down Syndrome by Altering Proteolytic Activity? Int J Mol Sci. 2018 Jan 15;19(1). pii: E248.

   "A number of pharmacologic options have been proposed to change the quality of life and lifespan of individuals with DS. It was reported that treatment with epigallocatechin gallate (EGCG) improves cognitive performance in animal models and in humans, suggesting that EGCG may alleviate symptoms of DS. Traditionally, EGCG has been associated with the ability to reduce dual specificity tyrosine phosphorylation regulated kinase 1A activity, which is overexpressed in trisomy 21. Based on the data available in the literature, we propose an additional way in which EGCG might affect trisomy 21-namely by modifying the proteolytic

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

activity of the enzymes involved. It is known that, in Down syndrome, the nerve growth factor (NGF) metabolic pathway is altered…, lowering the amount of mature NGF. EGCG inhibits MMP-9, thus protecting NGF. In this review, we describe mechanisms of proteolytic enzymes (MMP-9 and plasminogen activation system), their role in Down syndrome, their inhibition by EGCG, possible degradation of this polyphenol and the ability of EGCG and its degradation products to cross the blood-brain barrier. We conclude that known data accumulated so far provide promising evidence of MMP-9 inhibition by EGCG in the brain, which could slow down the abnormal degradation of NGF."

F. Studien zum Thema Folsäurestoffwechsel und Vitamin B12

1. Culp-Hill R. et al. Red blood cell metabolism in Down syndrome: hints on metabolic derangements in aging. Blood Adv. 2017 Dec 26; 1(27): 2776–2780.

   "Faster red blood cell (RBC) turnover may impact iron homeostasis and affect iron-dependent nonapoptotic cell death (ferroptosis), an etiological factor of Alzheimer's disease (AD), suggesting a potential therapeutic window, especially at an early age when the brain is still plastic, through dietary intervention with folinic acid, methyl-B12, thymidine, dimethylglycine, and/or methionine supplementation or iron metabolism management in children and adults with DS."

2. Fountoulakis M. et al. Overexpression of C1-tetrahydrofolate synthase in fetal Down syndrome brain. J Neural Transm Suppl. 2003;(67):85-93.

   "Several reports have been linking folate metabolism to DS and indeed, chromosome 21 even encodes for a specific folate carrier. The availability of brain tissue along with the advent of proteomics enabled us to identify and quantify C1-tetrahydrofolate synthase (THF-S), a key element in folate metabolism in brain along with other enzymes involved in C1-metabolism. Overexpression of this key enzyme in fetal DS brain at the early second trimester may indicate abnormal folate metabolism and may reflect folate deficiency. This may be of pathomechanistic relevance and thus extends and confirms the involvement of folate metabolism in trisomy 21."

3. Infantino V. et al. Impairment of methyl cycle affects mitochondrial methyl availability and glutathione level in Down's syndrome. Mol Genet Metab. 2011 Mar;102(3):378-82.

   "In the present study we find that the mitochondrial levels of S-adenosylmethionine are reduced in Down's syndrome compared to control cells demonstrating the effect of the methyl unbalance on mitochondria. The possible role of methylation in mitochondria is discussed and some preliminary results on a possible methylation target are presented.

4. Pogribna et al. Homocysteine metabolism in children with Down syndrome: in vitro modulation. Am J Hum Genet. 2001 Jul;69(1):88-95.

   "The results indicated that plasma levels of homocysteine, methionine, S-adenosylhomocysteine, and S-adenosylmethionine were all significantly decreased in

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

children with DS and that their lymphocyte DNA was hypermethylated relative to that in normal siblings. Plasma levels of cystathionine and cysteine were significantly increased, consistent with an increase in CBS activity. Plasma glutathione levels were significantly reduced in the children with DS and may reflect an increase in oxidative stress due to the overexpression of the superoxide dismutase gene, also located on chromosome 21. The addition of methionine, folinic acid, methyl-B(12), thymidine, or dimethylglycine to the cultured trisomy 21 lymphoblastoid cells improved the metabolic profile in vitro. The increased activity of CBS in children with DS significantly alters homocysteine metabolism such that the folate-dependent resynthesis of methionine is compromised. The decreased availability of homocysteine promotes the well-established "folate trap," creating a functional folate deficiency that may contribute to the metabolic pathology of this complex genetic disorder."

5. Varga P. et al. Biochemical alterations in patients with Down syndrome. Orv Hetil. 2008 Jun 29;149(26):1203-13.

"The lower homocysteine, folic acid and B 12 values may be considered as the consequence of an increased cystathionine-beta-synthase activity ("atheroma free model"). There was no significant alteration in antioxidant activity level. It can be supposed that the hydrogene peroxide produced due to increased expression of superoxide dismutase is metabolized by the induced glutathione-peroxidase and catalase keeping by this the balance of the antioxidant system. This hypothesis is supported by the normal N-acetyl-beta-D-glucosaminidase values not indicating any vascular damage. The high S100 values, however, reflect certain brain damage which shows a progress with the age. Based on these experiences, regular control of these parameters is recommended. Furthermore authors think that folic acid supplementation is indicated in order to improve the patients' learning capacity, inhibit the development of Alzheimer symptoms and improve the quality of life."

G. Studien zum Thema mitochondrielle Dysfunktion

1. Kidd PM. Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management. Altern Med Rev. 2005 Dec;10(4):268-93.

"Studies of the brain in Alzheimer's and other dementias, Down syndrome, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Friedreich's ataxia, aging, and constitutive disorders demonstrate impairments of the mitochondrial citric acid cycle and oxidative phosphorylation enzymes. Orthomolecular nutrients involved in mitochondrial metabolism provide clinical benefit. Among these are the essential minerals and the B vitamin group; vitamins E and K; and the antioxidant and energetic cofactors alpha-lipoic acid (ALA), ubiquinone (coenzyme Q10; CoQ10), and nicotinamide adenine dinucleotide, reduced (NADH). Recent advances in the area of stem cells and growth factors encourage optimism regarding brain regeneration. The trophic

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

nutrients acetyl L-carnitine (ALCAR), glycerophosphocholine (GPC), and phosphatidylserine (PS) provide mitochondrial support and conserve growth factor receptors; all three improved cognition in double-blind trials. The omega-3 fatty acid docosahexaenoic acid (DHA) is enzymatically combined with GPC and PS to form membrane phospholipids for nerve cell expansion. Practical recommendations are presented for integrating these safe and well-tolerated orthomolecular nutrients into a comprehensive dietary supplementation program for brain vitality and productive lifespan."

2. Valenti D. et al. The polyphenols resveratrol and epigallocatechin-3-gallate restore the severe impairment of mitochondria in hippocampal progenitor cells from a Down syndrome mouse model. Biochim Biophys Acta. 2016 Jun;1862(6):1093-104.

   "Mitochondrial dysfunctions critically impair nervous system development and are potentially involved in the pathogenesis of various neurodevelopmental disorders, including Down syndrome (DS), the most common genetic cause of intellectual disability. Previous studies from our group demonstrated impaired mitochondrial activity in peripheral cells from DS subjects and the efficacy of epigallocatechin-3-gallate (EGCG) - a natural polyphenol major component of green tea - to counteract the mitochondrial energy deficit. …These data point to a central role of mitochondrial dysfunction as an inherent feature of DS and not as a consequence of cell oxidative stress. Further, we disclose that, besides EGCG, also the natural polyphenol resveratrol, which displays a neuroprotective action in various human diseases but never tested in DS, restores oxidative phosphorylation efficiency and mitochondrial biogenesis, and improves proliferation of NPCs. This research paves the way for using nutraceuticals as a potential therapeutic tool in preventing or managing some energy deficit-associated DS clinical manifestations."

3. Valenti et al. Mitochondria as pharmacological targets in Down syndrome. Free Radic Biol Med. 2018 Jan;114:69-83.

   "We have analyzed the molecular determinants for mitochondrial dysfunctions and the resulting cellular reactive oxygen species (ROS) accumulation in Down Syndrome (DS). Many mitochondrial alterations in DS are shared with those found in other neurodegenerative diseases, aging, heart defects, and other disorders associated with DS clinical phenotype. We collected evidences demonstrating that mitochondrial alterations principally affect the brain, which is highly vulnerable to energy deficit and susceptible to oxidative stress. Therefore, we strongly propose that mitochondrial dysfunction may be a major etiological mechanism in intellectual disability and cognitive decline, which represent key hallmarks of DS. Therapeutic intervention aimed at improving mitochondrial function and reducing oxidative stress could be more effective during early childhood to prevent neurobehavioral outcomes. Therefore, natural bioactive compounds, such as polyphenols extracts, due to their long-term safety profile and efficacy could be strongly recommended as therapeutic interventions in DS. We also suggest that combinations of therapeutic agents may better improve outcomes in this complex disease."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

4. Zeevalk GD. et al. Mitochondrial inhibition and oxidative stress: reciprocating players in neurodegeneration. Antioxid Redox Signal. 2005 Sep-Oct;7(9-10):1117-39.

   "Although the etiology for many neurodegenerative diseases is unknown, the common findings of mitochondrial defects and oxidative damage posit these events as contributing factors. The temporal conundrum of whether mitochondrial defects lead to enhanced reactive oxygen species generation, or conversely, if oxidative stress is the underlying cause of the mitochondrial defects remains enigmatic. This review focuses on evidence to show that either event can lead to the evolution of the other with subsequent neuronal cell loss. Glutathione is a major antioxidant system used by cells and mitochondria for protection and is altered in a number of neurodegenerative and neuropathological conditions. This review also addresses the multiple roles for glutathione during mitochondrial inhibition or oxidative stress. Protein aggregation and inclusions are hallmarks of a number of neurodegenerative diseases. Recent evidence that links protein aggregation to oxidative stress and mitochondrial dysfunction will also be examined. Lastly, current therapies that target mitochondrial dysfunction or oxidative stress are discussed."

H. Studien zum Thema pränatale Behandlung

1. Baggot PJ. and Baggot RM. Fetal Therapy for Down Syndrome: Report of Three Cases and a Review of the Literature. Issues Law Med. 2017 Spring;32(1):31-41.

   "Neurogenesis (replication, survival, and organization of neurons) may be enhanced in many ways. Case reports suggest that several nutrients and drugs are promising. Experiments with mouse models may lead to effective treatments. Proper timing of treatment is crucial. Better understanding of brain development could benefit all children, not just those with Down syndrome."

2. Blusztajn JK. and Mellott TJ. Neuroprotective actions of perinatal choline nutrition. Clin Chem Lab Med. 2013 Mar 1; 51(3): 591–599.

   "Choline is an essential nutrient for humans. Studies in rats and mice have shown that high choline intake during gestation or the perinatal period improves cognitive function in adulthood, prevents memory decline of old age, and protects the brain from damage and cognitive and neurological deterioration associated with epilepsy and hereditary conditions such as Down's and Rett syndromes. These behavioral changes are accompanied by modified patterns of expression of hundreds of cortical and hippocampal genes including those encoding proteins central for learning and memory processing. The effects of choline correlate with cerebral cortical changes in DNA and histone methylation, thus suggesting an epigenomic mechanism of action of perinatal choline."

3. Guedj et al. Prenatal treatment of Down syndrome: a reality? Curr Opin Obstet Gynecol. 2014 Apr;26(2):92-103.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"This review summarizes the different functional abnormalities targeted by researchers in mouse models of Down syndrome. Three main strategies have been used: neural stem cell implantation; environmental enrichment and physical exercise; and pharmacotherapy. Pharmacological targets include the choline pathway, GABA and NMDA receptors, DYRK1A protein, oxidative stress and pathways involved in development and neurogenesis. Many strategies have improved learning and memory as well as electrophysiological and molecular alterations in affected animals. To date, eight molecules have been tested in human adult clinical trials. No studies have yet been performed on infants. However, compelling studies reveal that permanent brain alterations originate during fetal life in Down syndrome. Early prenatal diagnosis offers a 28 weeks window to positively impact brain development and improve postnatal cognitive outcome in affected individuals. Only a few approaches (Epigallocatechine gallate, NAP/SAL, fluoxetine, and apigenin) have been used to treat mice in utero; these showed therapeutic effects that persisted to adulthood."

4. Perrone S. et al. Early oxidative stress in amniotic fluid of pregnancies with Down syndrome. Clin Biochem. 2007 Feb;40(3-4):177-80.

   "The study reveals that oxidative stress occurs early in pregnancy and supports the idea of testing whether prenatal antioxidant therapy may prevent or delay the onset of oxidative stress diseases in the DS population."

5. Stagni F. et al. Timing of therapies for Down syndrome: the sooner, the better. Front Behav Neurosci. 2015; 9: 265.

   "Since brain alterations in DS start to be present prenatally, the prenatal period represents an optimum window of opportunity for therapeutic interventions. Importantly, recent studies clearly show that treatment during the prenatal period can rescue overall brain development and behavior and that this effect outlasts treatment cessation. Although late therapies are unlikely to exert drastic changes in the brain, they may have an impact on the hippocampus, a brain region where neurogenesis continues throughout life. Indeed, treatment at adult life stages improves or even rescues hippocampal neurogenesis and connectivity and hippocampal-dependent learning and memory, although the duration of these effects still remains, in the majority of cases, a matter of investigation. The exciting discovery that trisomy-linked brain abnormalities can be prevented with early interventions gives us reason to believe that treatments during pregnancy may rescue brain development in fetuses with DS."

6. Strupp et al. Maternal Choline Supplementation: A Potential Prenatal Treatment for Down Syndrome and Alzheimer's Disease. Curr Alzheimer Res. 2016;13(1):97-106.

   "A potential therapeutic strategy emerging from the study of trisomic mouse models of DS is to supplement the maternal diet with additional choline during pregnancy and lactation. Studies demonstrate that maternal choline supplementation (MCS) markedly improves spatial cognition and attentional function, as well as normalizes adult hippocampal

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

neurogenesis and offers protection to basal forebrain cholinergic neurons (BFCNs) in the Ts65Dn mouse model of DS. These effects on neurogenesis and BFCNs correlate significantly with spatial cognition, suggesting functional relationships. In this review, we highlight some of these provocative findings, which suggest that supplementing the maternal diet with additional choline may serve as an effective and safe prenatal strategy for improving cognitive, affective, and neural functioning in DS. “

I. Studien zum Thema Polyphenole, Resveratrol und Curcumin

1. Carvalho AN. et al. Oxidative Stress and Antioxidants in Neurological Diseases: Is There Still Hope? Curr Drug Targets. 2017 Mar 30;18(6):705-718.

   "...compounds that stimulate the expression of endogenous antioxidants by activation of the Nrf2 pathway such as curcumin, dimethyl fumarate, resveratrol and sulforaphane could represent promising approaches for management of these devastating diseases.”

2. Li YY. et al. miRNA-155 upregulation and complement factor H deficits in Down's syndrome.Neuroreport. 2012 Feb 15;23(3):168-73.

   “These findings suggest that immunopathological deficits associated with Down's syndrome can, in part, be explained by a generalized miRNA-155-mediated downregulation of complement factor H (CFH) that may contribute to both brain and systemic immune pathology.”

3. Lopez-Ramirez MA. et al. MicroRNA-155 negatively affects blood-brain barrier function during neuroinflammation. FASEB J. 2014 Jun;28(6):2551-65.

   “We propose that brain endothelial miR-155 is a negative regulator of blood-brain barrier (BBB) function that may constitute a novel therapeutic target for CNS neuroinflammatory disorders.”

4. Michaille JJ. et al. Medicines (Basel). 2018 Jul 9;5(3). MiR-663, a MicroRNA Linked with Inflammation and Cancer That Is under the Influence of Resveratrol.

   “Given that Resveratrol (RSV) seems to be active while provided at low dose for a sustained period, rather than at higher doses for a shorter period, it is possible that the wide range of beneficial properties of this plant polyphenol may rely on its capacity to simultaneously reset the expression of multiple microRNAs within a range of concentrations where they would work for the health of the organism, rather than just sharply increasing or decreasing their expression.”

5. Milenkovic D. et al. miRNA as molecular target of polyphenols underlying their biological effects.Free Radic Biol Med. 2013 Sep;64:40-51.

   „Taken together, the data generated from these studies reveal the capacity of dietary polyphenols to modulate expression of miRNA and provide insights of new mechanisms of action of these bioactive compounds underlying their beneficial health properties.”

6. Moosavi F. et al. Modulation of neurotrophic signaling pathways by polyphenols. Drug Des Devel Ther. 2016; 10: 23–42.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"Polyphenols are an important class of phytochemicals, and several lines of evidence have demonstrated their beneficial effects in the context of a number of pathologies including neurodegenerative disorders such as Alzheimer's and Parkinson's disease. In this report, we review the studies on the effects of polyphenols on neuronal survival, growth, proliferation and differentiation, and the signaling pathways involved in these neurotrophic actions."

7. Poulose SM. et al. Nutritional Factors Affecting Adult Neurogenesis and Cognitive Function. Adv Nutr. 2017 Nov 15;8(6):804-811.

   "Adult neurogenesis, a complex process by which stem cells in the hippocampal brain region differentiate and proliferate into new neurons and other resident brain cells, is known to be affected by many intrinsic and extrinsic factors, including diet. Neurogenesis plays a critical role in neural plasticity, brain homeostasis, and maintenance in the central nervous system and is a crucial factor in preserving the cognitive function and repair of damaged brain cells affected by aging and brain disorders. Intrinsic factors such as aging, neuroinflammation, oxidative stress, and brain injury, as well as lifestyle factors such as high-fat and high-sugar diets and alcohol and opioid addiction, negatively affect adult neurogenesis. Conversely, many dietary components such as curcumin, resveratrol, blueberry polyphenols, sulforaphane, salvionic acid, polyunsaturated fatty acids (PUFAs), and diets enriched with polyphenols and PUFAs, as well as caloric restriction, physical exercise, and learning, have been shown to induce neurogenesis in adult brains."

8. Vacca RA. et al. Plant polyphenols as natural drugs for the management of Down syndrome and related disorders.Neurosci Biobehav Rev. 2016 Dec;71:865-877.

   "Polyphenols are secondary metabolites of plants largely found in fruits, vegetables, cereals and beverages, and therefore represent important constituents of the human diet. Increasing studies have demonstrated the potential beneficial effects of polyphenols on human health. Extensive reviews have discussed the protective effects of polyphenols against a series of diseases such as cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders. Limited studies have investigated the potential therapeutic effects of these natural compounds on neurodevelopmental disorders associated with intellectual disability, such as Down syndrome (DS), for which mitochondrial dysfunctions and oxidative stress are hallmarks and contribute to the deleterious symptoms and cognitive decline. This review, starting from the structure, source, bioavailability and pharmacokinetics of relevant polyphenols, highlights recent studies on the effect and potential molecular mechanism(s) of action of the phenolic compounds epigallocatechin-3-gallate, resveratrol and hydroxytyrosol in restoring mitochondrial energy deficit and in reversing phenotypical alteration in DS. The clinical implications of plant polyphenol dietary supplements as therapeutic tools in managing DS and other intellectual disability-related diseases, is also discussed."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

J. Studien zum Thema Schilddrüsenfunktion

1. Blehaut H. et al. Effect of leucovorin (folinic acid) on the developmental quotient of children with Down's syndrome (trisomy 21) and influence of thyroid status. PLoS One. 2010 Jan 11;5(1):e8394.

   "These results suggest that leucovorin improves the psychomotor development of children with Down's syndrome, at least in some subgroups of the DS population, particularly those on thyroxin treatment."

2. Cebeci AN. et al. Profile of Hypothyroidism in Down's Syndrome. J Clin Res Pediatr Endocrinol. 2013 Jun; 5(2): 116–120.

   "…we found a high prevalence of thyroid dysgenesis in DS patients with permanent thyroid dysfunction. This association has not been reported before, so further studies investigating the thyroid gland size with ultrasound technique need to be performed to confirm our results. We suggest that all patients with DS should be screened for thyroid dysgenesis, and if present, lifelong treatment with L-T4 should immediately be started."

3. Kanavin et al. Thyroid hypofunction in Down's syndrome: is it related to oxidative stress? Biol Trace Elem Res. 2000 Winter;78(1-3):35-42.

   "Our results support the suggestion that thyroid hypofunction in patients with Down's syndrome in some way is linked to the low serum levels of selenium found in these patients. It is suggested that selenium-containing proteins are involved in thyroid hormonal synthesis, by protecting biosynthetic processes against the toxicity of free oxygen radicals."

4. Purdy IB. et al. Revisiting early hypothyroidism screening in infants with Down syndrome. J Perinatol. 2014 Dec;34(12):936-40.

   "Despite normal newborn screens, the incidence of any hypothyroidism (early compensated hypothyroidism and primary hypothyroidism) was higher than previously reported."

5. Thiel, R., Fowkes, SW. Down syndrome and thyroid dysfunction: should nutritional support be the first-line treatment? Med Hypotheses. 2007;69(4):809-15. Epub 2007 Mar 26.

   "As nutrition for those with DS has been safely used by some practitioners for many decades, it is suggested that nutritional thyroid support, and not necessarily thyroxine, should be considered for use as a first line treatment for those with trisomy 21. This paper also hypothesizes that nutritional interventions begun prenatally by the mother, may possibly also be of benefit."

6. van Trotsenburg AS. et al. The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial. J Clin Endocrinol Metab. 2005 Jun;90(6):3304-11.

   "Young Down syndrome children appear to have a mild form of congenital hypothyroidism that is rarely detected by neonatal screening and usually left untreated. The data of our study provide evidence to support the hypothesis that thyroxine treatment may improve development and growth of young Down syndrome children. Thyroxine treatment should be considered in Down syndrome neonates to maximize their early development and growth."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

K. Studien zum Thema Behandlung mit TNI/Nutrivene und andere

1. De Falco FA. et al. Effect of the chronic treatment with L-acetylcarnitine in Down's syndrome. Clin Ter. 1994 Feb;144(2):123-7.

   "Neuropsychologic tests were performed in subjects with Down syndrome in order to assess the effect of a 90-day treatment with L-acetyl-carnitine (LAC). …Treated Down syndrome patients showed statistically significant improvements of visual memory and attention both in absolute terms and in comparison with the other groups. No improvement was found in mentally deficient non-Down subjects, so that the favourable effect of LAC appears to be specific for Down patients. In view of the analogies of the pathology and neurochemistry between Down syndrome and Alzheimer degenerative deficiency (deficit of cholinergic transmission) it is suggested that the action of LAC in these pathologies is related to its direct and indirect cholinomimetic effect."

2. Gelb, MJ. Targeted Nutritional Intervention (TNI) for Children with Down Syndrome. Pädiat. Prax. 59: 703-708 (2001)

   "In the current study, I report on the effects of TNI supplementation for more than 12 months. I observed a reduction of infections, increases in percentile ranking of growth and improvement and normalization of various laboratory parameters. Parents and therapists have reported considerable improvements in the behaviour, cooperation and development of children adminstered TNI supplementation."

3. Hart SJ. et al. Pharmacological interventions to improve cognition and adaptive functioning in Down syndrome: Strides to date. Am J Med Genet A. 2017 Nov;173(11):3029-3041.

   "Despite the increased knowledge about cognition in DS, the body of research, to date, has significant limitations, including a focus on older study participants, limited information about reliability or suitability of study measures, and heterogeneity among individuals in study populations. Future research focusing on earlier interventions, development of appropriate outcome measures, identification of potential sub-groups of responders to interventions, and collaboration between industry, academia, advocacy, and regulatory groups will be important for addressing limitations and moving toward development of potential effective interventions for cognition in DS."

4. Mazurek D., Wyka J. Down syndrome--genetic and nutritional aspects of accompanying disorders. Rocz Panstw Zakl Hig. 2015;66(3):189-94.

   "Vitamin B group deficiencies and abnormal blood homocysteine levels decrease the rate of intellectual development in Down Syndrome (DS) cases. Zinc deficiencies result in short stature, thyroid function disorders and an increased appetite caused by excessive supplementation. Scientific advances in the research and diagnosis of DS, as well as preventing any associated conditions, have significantly increased life expectancies of those with this genetic disorder. Early dietary interventions by parents or guardians of DS children afford an opportunity for decreasing the risk or delaying some of the DS associated conditions from appearing, thus beneficially impacting on their quality of life."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

5. Meguid et al. Antioxidant activity in Egyptian children with Down syndrome before and after nutritional supplementation. J. Chem. Pharm. Res., 2015, 7(2):324-331

   "Before nutritional supplementation, GSH and GST levels were significantly low, while SOD levels in DS children were significantly high compared to controls. After 6 months supplementation, significant high levels were observed in the activity of GPx and CAT with elevated GPx/GR ratio and reduced SOD/(CAT + GPx) ratio among DS children.
   Supplementation of DS children with formula X (Nutrivene) is important at early years of life, as it may protect against harmful oxidative damage."
6. Seven M. et al. Plasma carnitine levels in children with Down syndrome. Am J Hum Biol. 2001 Nov-Dec;13(6):721-5.

   "Carnitine is responsible for several chemical processes, including lipid metabolism, nerve cell conduction, reduction in muscle hypotonia, and limitation in oxidative damage to cells. In patients with Down syndrome (DS), the process of growth is behind that of normal children and neuromuscular control is attained somewhat later. … Carnitine level was significantly lower in DS patients compared with normal children between 6 months to 5 years of age. Between 5 and 13 years of age, the level of carnitine was about the same in both the normal and DS groups. The results suggest that carnitine level shows a different pattern of age related increase in DS compared to normal children."
7. Zubillaga P. et al. Effect of vitamin D and calcium supplementation on bone turnover in institutionalized adults with Down's Syndrome. Eur J Clin Nutr. 2006 May;60(5):605-9.

   "The results obtained allow to include people with DS as a risk group with regards to vitamin D deficit, which that can be corrected with vitamin D and calcium supplementation, and giving rise to an improvement of the biochemical markers related to the phospho-calcium metabolism and bone remodelling."

L. Studien zum Thema Zink

1. Bucci et al. Zinc sulfate supplementation improves thyroid function in hypozincemic Down children. Biol Trace Elem Res. 1999 Mar;67(3):257-68.

   "In subjects affected by trisomy 21 (Down syndrome), hypothyroidism is the most common endocrinological deficit. Plasma zinc levels, which are commonly detected below the normal range in Down patients, are related to some endocrinological and immunological functions; in fact, zinc deficiency has been shown to impair immune response and growth rate. After 6 mo of supplementation, an improvement of thyroid function was observed in hypozincemic patients. At the end of the study, TSH significantly decreased in treated hypozincemic subjects (4.48 +/- 1.93 vs 2.96 +/- 1.20 mUI/mL) and it was no longer different in comparison to normozincemic patients. We suggest zinc supplementation to the diet in hypozincemic Down children as a simple and useful therapeutic tool."
2. Chiricolo et al. Enhanced DNA repair in lymphocytes of Down syndrome patients: the influence of zinc nutritional supplementation. Mutat Res. 1993 Aug;295(3):105-11.

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

"Oral zinc supplementation is able to correct zinc deficiency and some immune defects present in Down's syndrome (DS), while other beneficial effects can be predicted because of the broad spectrum of biochemical pathways and the great variety of enzymes which depend on zinc bio-availability. In comparison with lymphocytes from normal children the DNA damage induction after ionizing radiation in DS lymphocytes both before and after zinc supplementation was normal. On the other hand, the rate of DNA repair in DS was highly and significantly accelerated before zinc treatment. After supplementation with zinc sulfate, the DNA repair rate was consistently slowed down becoming similar to that of control subjects. This is the first demonstration that a nutritional intervention in humans is apparently able to modify the biochemical steps which control the rate of DNA repair."

3. Licastro F. et al. Zinc affects the metabolism of thyroid hormones in children with Down's syndrome: normalization of thyroid stimulating hormone and of reversal triiodothyronine plasmic levels by dietary zinc supplementation. Int J Neurosci. 1992 Jul-Aug;65(1-4):259-68.

   "The increased efficiency of the immune system and the normalization of some endocrine parameters by zinc supplementation suggests that zinc deficiency may play a crucial role in some of the pathological manifestations associated with the syndrome, such as infections and malfunctioning of the thyroid gland."

4. Licastro et al. Oral zinc supplementation in Down's syndrome subjects decreased infections and normalized some humoral and cellular immune parameters. J Intellect Disabil Res. 1994 Apr;38 (Pt 2):149-62.

   "The effect of 4 months of oral zinc supplementation on immune functions in non-institutionalized young female and male Down's syndrome (DS) subjects was studied. Some immune parameters were significantly influenced by zinc treatment. In particular, a normalization of thymulin and zinc plasma levels were found in these subjects after zinc supplementation. At the end of the clinical trial, in vitro lymphocyte proliferation and polymorphonuclear activity also increased and reached normal values. Zinc administration exerted a positive clinical effect in these children, since a reduced incidence of infections was found."

5. Lima et al. Nutritional status of zinc in children with Down syndrome. Biol Trace Elem Res. 2010 Jan;133(1):20-8. doi: 10.1007/s12011-009-8408-8. Epub 2009 May 26.

   "Zinc concentrations were significantly lower in plasma and urine and higher in erythrocytes of children with DS. The results allowed us to conclude that the altered zinc nutritional status of individuals with Down syndrome contributes to clinical disturbances that usually appear with aging in these patients."

6. Napolitano G. et al. Growth delay in Down syndrome and zinc sulphate supplementation. Am J Med Genet Suppl. 1990;7:63-5.

   "Children affected with Down syndrome (DS) show deficient growth, immunodeficiency--especially concerning the T-cell population--and low plasma zinc levels. …In conclusion, zinc sulphate therapy of patients with DS affects not only the immune system, as previously reported, but can also accelerate growth."

Dr. rer. nat. Petra Buchanan Stechertweg 29 0761/38 488 944 www.praxis321.de
Heilpraktikerin 79104 Freiburg info@praxis321.de

Dr. rer. nat. Petra Buchanan
Heilpraktikerin
Stechertweg 29
79104 Freiburg
0761/38 488 944
info@praxis321.de
www.praxis321.de